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Full Length Article

Incidence of venous thromboembolism in patients with non-Hodgkin lymphoma

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ABSTRACT

Introduction: Patients with non-Hodgkin lymphoma (NHL) have an increased risk of venous thromboembolism (VTE). Current risk-prediction models classify NHL as a single entity. We aimed to quantify the difference in VTE risk in follicular lymphoma (FL) versus diffuse large B cell lymphoma (DLBCL).

Methods: Using a prospective cohort study, we identified 2730 patients (2037 DLBCL; 693 FL) within the Veteran's Administration Central Cancer Registry. A competing risk model assessed the association between VTE risk and histology in the first year after NHL diagnosis. We assessed the effect of additional risk factors for VTE in NHL.

Results: In univariate analysis, DLBCL was associated with increased risk of VTE compared to FL in the first year after diagnosis; this association was no longer significant in adjusted analysis (adjusted hazard ratio (aHR) 1.52; 95% CI 0.97–2.40). Major risk factors for VTE included history of VTE before NHL diagnosis (aHR 4.73, $p \leq 0.0001$) and time period during chemotherapy administration (aHR 7.60, $p \leq 0.0001$). Additional risk factors included: stage III/IV disease ($p = 0.02$), BMI ≥ 30 ($p = 0.02$), B-symptoms ($p = 0.02$), and doxorubicin ($p = 0.04$). The cumulative incidence of VTE was highest in the period following diagnosis and decreased over time for both histologies.

Conclusion: DLBCL is associated with increased risk of VTE compared to FL. This risk is markedly attenuated when adjusting for additional risk factors. The strongest predictors for development of VTE included: time period during chemotherapy administration (especially doxorubicin) and history of VTE. This knowledge can assist clinicians in identifying NHL patients at high risk for VTE.

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1. Introduction

Venous thromboembolism (VTE) is a leading cause of death in patients with cancer [1,2]. The American Society of Clinical Oncology (ASCO) recommends routine assessment of thrombosis risk in patients with newly diagnosed cancer and suggests use of a validated VTE risk prediction model [3,4]. Patients with hematologic malignancies, such as non-Hodgkin lymphoma (NHL), have an increased risk of VTE [5–7]. VTE risk prediction models aggregate all NHL as a single risk cohort [4,8,9]; however, recent studies suggest that the rate of VTE differs based on NHL histology, with the highest rates in aggressive lymphomas, such as diffuse large B cell lymphoma (DLBCL) [10–15].

Given the apparent heterogeneity of VTE risk in NHL, using available prediction models that define NHL as a homogenous disease may over- or under-estimate VTE risk. Misclassification of risk can unnecessarily expose low-risk patients to thromboprophylaxis, or lead to failure to prescribe thromboprophylaxis in high-risk patients. Understanding VTE risk in NHL can allow for more accurate stratification of VTE risk in prediction models and facilitate identification of patients who may benefit from thromboprophylaxis [16,17].

Here, we use a large cancer-registry to compare VTE risk between follicular lymphoma (FL), the most common indolent NHL, versus DLBCL, the most common aggressive NHL. In addition, we identify clinical and laboratory risk factors associated with VTE in NHL. To allow for identification of the period during which thromboprophylaxis would have the greatest benefit, we describe the timing of thrombosis in NHL.

2. Methods

2.1. Study cohort

We assembled a cohort of patients diagnosed between October 1, 1998 and December 31, 2009, using *International Classification of Disease*-O3 (ICD-O3) codes from the Veterans Administration Central Cancer Registry (VACCR), with DLBCL (I-O3 codes 9680 or 9684) or FL (ICD-O3 codes 9690, 9691, 9695, 9698). To eliminate confounding based on

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treatment, we excluded patients who did not receive treatment or who received treatment regimens other than CHOP (cyclophosphamide, adriamycin, vincristine, prednisone)-like regimens. We also excluded patients with primary central nervous system DLBCL. Patients were followed from time of diagnosis until development of VTE, death, or loss to follow up; whichever came first. In the VTE analysis, we censored patients at the time of death or loss to follow up. Institutional Review Boards of the Veterans Health Administration (VHA) Saint Louis Medical Center and Washington University School of Medicine approved the study prior to chart review.

2.2. Measurements

We extracted data on sex, race, lactate dehydrogenase (LDH), hemoglobin (HGB), NHL histology, stage, B-symptoms, body mass index (BMI), medical co-morbidities, chemotherapy use, and occurrence of VTE. We identified B-symptoms (defined as the presence of fever (>38 °C), drenching night sweats, or ≥10% loss in body weight in the 6 months preceding diagnosis) using a combination of VACCR data, structured manual review of provider clinical notes, and vital sign data. We calculated the Romano adaptation of the Charlson comorbidity index for each patient at the time of diagnosis using ICD-9 codes [18]. We identified administration of chemotherapy with CHOP or CHOP-like regimens ± rituximab using Pharmacy Benefits Management (PBM) records. Time during chemotherapy administration was defined as PBM record of the first dose of chemotherapy prescription until plus 30 days past the last dose of chemotherapy. We identified VTE, defined as deep vein thrombosis (DVT), pulmonary embolism (PE), or both DVT and PE, by using a validated algorithm that requires an ICD-9 diagnostic code for VTE plus either anticoagulant therapy, common procedural terminology (CPT) code for placement of a vena-cava filter, or death within 30 days of ICD-9 diagnosis of VTE [19]. History of VTE could occur at any time before NHL diagnosis. To prevent false positive diagnoses caused by anticoagulant therapy for atrial fibrillation, we manually extracted charts of these patients (ICD-9 code 427.31) and reviewed the results for objective VTE testing (Doppler venous ultrasound, venography, pulmonary embolism protocol computerized tomography (CT), CT angiography, and ventilation perfusion scans).

2.3. Statistical analyses

We compared baseline characteristics between the DLBCL and FL groups using Chi-square and Cochran-Mantel-Haenszel tests on categorical variables and the unpaired Student's *t*-test on continuous variables. The primary objective of the study was to determine the risk of VTE in patients with DLBCL compared to FL within one year after the diagnosis of lymphoma. The association between VTE within the first year of NHL diagnosis and candidate risk factors, including histology, was assessed with univariate analysis reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The associations were then assessed using multivariate analysis with a competing risks model using the methods of Fine and Gray, accounting for death as a competing risk [20]. Candidate risk factors included: histology (DLBCL versus FL), history of prior VTE, BMI, age, race, Charlson co-morbidity score, HGB < 10 g/dL, elevated LDH, stage (stage III/IV versus I/II), presence of B-symptoms, treatment with doxorubicin, and time period during chemotherapy administration. To preserve sample size and to minimize bias, we included records with sparse missing data by creating "unknown" categories.

We calculated cumulative incidence rates of VTE in NHL per 1000 person-years over pre-specified time intervals following NHL diagnosis (0–30 days, 31–180 days, 181–365 days). Time intervals were selected based on expected clinical management course. The interval of 0–30 days was selected to represent the time period when ancillary studies were likely being done prior to therapy initiation. Given the knowledge of treatment regimens included, most patients would be off chemotherapy by 181–365 days post diagnosis. We compared rates of VTE between DLBCL and FL with confidence intervals constructed using Poisson distribution and test-based methods using annualized incidence [21]. A two-tailed alpha significance level of <0.05 was used for all analyses. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

A total of 4570 patients with NHL were identified (2839 DLBCL; 1731 FL), of whom 1803 were excluded for not receiving treatment, receiving treatment outside of the VHA health system, or for receiving non-CHOP or CHOP-like therapy. Of the remaining 2767 patients, 37 were excluded for unknown lymphoma stage. The final analytic cohort consisted of 2730 patients (2037 DLBCL; 693 FL) (Fig. 1). The mean age at NHL diagnosis was 64 years, with the majority of the patients being male (97%), Caucasian (88%), and with a diagnosis of DLBCL (75%) (Table 1). The mean time from diagnosis to treatment initiation was 2.0 months for the entire cohort, but differed by histology: 1.3 months for DLBCL and 3.9 months for FL. During the entire follow-up period, there were 246 VTEs (192 DLBCL; 54 FL). Within the first year of NHL diagnosis, 181 patients experienced VTE (151 DLBCL; 30 FL); of which there were 34 PE, 121 DVT, and 26 with PE + DVT. Of the 151 DLBCL patients who experienced a VTE after NHL diagnosis, 9 had a history of prior VTE; while of the 30 FL patients who experienced a VTE, 1 had a history of prior VTE. The median follow-up time for the cohort was 28.4 months.

In the first 12-months following NHL diagnosis, there was an increased risk of VTE in patients with DLBCL versus those with FL with an unadjusted HR (95% CI) of 1.74 (1.18–2.58) (Table 2); however after adjusting for additional risk factors, this finding was no longer significant (adjusted HR (aHR) 1.52; 95% CI 0.97–2.40) (Table 3). Risk factors in multivariate analysis for development of VTE in patients with DLBCL or FL were: history of VTE before lymphoma diagnosis (aHR 4.73, 95% CI 2.47–9.04), time during chemotherapy administration (aHR 7.60; 95% CI 4.71–12.25), stage III/IV disease (aHR 1.49, 95% CI 1.05–2.10), BMI ≥ 30 (aHR 1.60, 95% CI 1.08–2.37), presence of B-symptoms (aHR 1.45, 95% CI 1.06–2.02), and use of doxorubicin (aHR 1.96, 95% CI 1.03–3.72) (Table 2). There was a possible trend toward an association between VTE and HGB < 10 g/dL (aHR 1.48, $p = 0.08$). There was no significant association between risk of VTE and age, race, elevated LDH, higher comorbidity index, BMI < 18.5, or 25 < BMI ≤ 30 in multivariate analysis.

VTE = venous thromboembolism; NHL = Non-Hodgkin lymphoma; BMI = body mass index; HGB = hemoglobin; LDH = lactate dehydrogenase; ULN = upper limit of normal; B-symptoms = fever (>38 °C),

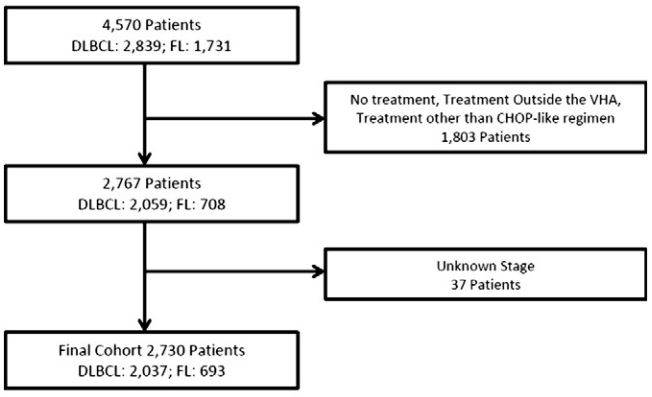

Fig. 1. Consort diagram, DLBCL/FL between 1998 and 2008 treated with *R*-CHOP/CHOP-like Regimens.