Thrombosis Research 156 (2017) 14–19

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Recurrence of venous thromboembolism among adults acute leukemia patients treated at the University of Texas MD Anderson Cancer Center: Incidence and risk factors

Nhiem V. Luong [a,*], Michael H. Kroll [b], Khanh Vu [c]

[a] Division of Public Health, Office of Infectious Disease Epidemiology, Delaware Health and Social Services, Dover, DE, USA
[b] Department of Pulmonary Medicine, Section of Thrombosis and Benign Hematology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Article history:
Received 28 November 2016
Received in revised form 5 May 2017
Accepted 20 May 2017
Available online 24 May 2017

Keywords:
Acute leukemia
Cancer
Thrombosis
Venous thromboembolism
Recurrence

ABSTRACT

The purpose was to determine the incidence and risk factors for venous thromboembolism (VTE) recurrence among adult acute leukemia patients. We performed a retrospective study of adult acute leukemia patients who were treated at our institution between November 1999 and May 2005. Medical records of 139 patients with an initial VTE were reviewed and followed up to May 2010 for VTE recurrence. Of these 139 patients [86 with acute myelogenous leukemia (AML), 53 with acute lymphocytic leukemia (ALL)], 27 (19.4%, 16 AML and 11 ALL) had VTE recurrence. The overall incidence rate of VTE was 8.6 per 100 person-years (median follow-up time: 0.9 years). It was 5.9 and 12.4 per 100 person-years among ALL and AML patients, respectively. The cumulative proportion of recurrent VTE was 2.16%, 10.9%, 16.6%, 25.9%, 30.6%, and 34.2% at 1 month, 6 months, 1 year, 3 years, 5 years, and 7 years, respectively. In a multivariate Cox hazards model, significant predictors for VTE recurrence included catheter thrombosis [adjusted hazard ratio (aHR)]:6.3, 95%CI:1.17–34.0), prior history of hematologic cancer (aHR:4.2, 95%CI:1.5–11.2), chronic lung disease (aHR: 3.4, 95%CI:0.92–12.5), psychological disorder (aHR: 4.3, 95%CI:1.5–12.2), and liver disease (aHR: 3.8, 95%CI: 1.04–14.3). VTE recurrence is common among adult acute leukemia patients and it continues up to 7 years after the initial episode. Catheter thrombosis, a history of hematologic malignancy antecedent to acute leukemia, and lung, liver and psychiatric co-morbidities increase the patient risk for VTE recurrence. Further studies should be conducted to improve the prevention of VTE recurrence in leukemia patients.

1. Introduction

Venous thromboembolism (VTE) is one of the most common complications in patients with malignancies [1–3]. Heit et al. indicate that patients receiving chemotherapy have a 6.5-fold increased risk for VTE [4]. Blom et al. indicate that patients with hematological malignancies are approximately 26 times more likely to develop VTE in comparison with the general population [2]. Recent studies report a high rate of thrombosis in acute leukemia patients; this rate can vary from 1.4% to 9.6% at or before diagnosis and from 1.7% to 12% during therapy [5–11].

After the first episode of cancer-associated VTE, patients are usually treated with anticoagulation for at least 6 to 12 months [12,13]. However, this is often difficult for acute leukemia patients because of thrombocytopenia and concerns about the risk of bleeding when thrombocytopenic patients receive therapeutic anticoagulation [14–17]. We observed that VTE recurred in 20.7% of ALL patients and 18.6% of AML patients, almost all of whom were off anticoagulation at the time of recurrence [10]. The aim of this analysis is to determine the incidence of VTE recurrence, clarify the therapeutic index of anticoagulation in thrombocytopenic leukemics, and to identify potentially actionable factors contributing to recurrent VTE in patients with acute leukemia.

2. Methods

2.1. Study design and patients

Medical records of 139 acute leukemia patients with an initial episode of VTE, including 53 patients with acute lymphoblastic leukemia (ALL) and 86 patients with acute myelogenous leukemia (AML) who were admitted into MD Anderson Cancer Center for treatment during a period from November 1999 to May 2005, were reviewed and

* Corresponding author at: Division of Public Health, Office of Infectious Disease Epidemiology, Delaware Health and Social Services, #248, Jesse Cooper Building, 417 Federal Street, Dover, DE 19901, USA.
E-mail address: Nhiem.luong@state.de.us (N.V. Luong).

http://dx.doi.org/10.1016/j.thromres.2017.05.019
0049-3848/

analyzed. Their medical charts were identified, retrospectively reviewed, and tracked up until May 2010 for VTE recurrence.

2.2. Study end points

VTE recurrence is the endpoint of the study. It could be pulmonary embolism (PE) or deep venous thrombosis (DVT). Cases of VTE were detected and confirmed using clinical documentation and results from diagnostic imaging studies such as venogram, color Doppler sonography/Duplex ultrasound, ventilation-perfusion lung scan, or chest computed tomographic (CT) scan/CT angiogram. Recurrence of VTE was determined if the patient developed a VTE in a venous system different from the initial event or if there was extension of the original thrombus >3 months after documentation of the original thrombosis. Patients were classified as having upper extremity DVT, lower extremity DVT, or PE, and catheter thromboses were identified. Patients with both PE and DVT (upper or lower extremity DVT) were classified as having PE and the locations of the DVT described.

Data on VTE and other variables were retrieved from the institution's patient electronic medical records including demographics (e.g. age, gender, ethnic group); baseline laboratory findings and clinical parameters (e.g. BMI, weight, height, platelet count, white blood cell, fibrinogen, PT, PTT, creatinine, cytogenetics); co-morbidities (e.g. other malignancies, varicose veins/phlebitis, diabetes, hypertension, dyslipidemia, hematological disorders, pulmonary, renal, hepatic, gastrointestinal, endocrine, diseases of bone/joint, neurological, psychological, urological disorders); prior history of VTE; smoking status; catheter placement (yes/no) during the last three months; and anticoagulation treatment.

2.3. Statistical methods

A statistical power analysis was performed for sample size estimation using methods appropriate for the Cox Proportional Hazards Regression [18]. The calculation, with a power of 0.80 and a two-sided alpha of 0.05, was based on the cumulative incidence of recurrent thromboembolism of 20.7% at 12-months and a hazard ratio of 3.2 for recurrent VTE in patients with cancer. Data was censored at the earliest death or May 2010, whichever came first. It was determined that a sample size of 113 with 24 outcome events were required. Aiming at obtaining a larger sample size, with an estimated attrition rate of <1% based on our prior experience, 139 patients with an initial episode of VTE were included in the study.

To describe patient demographics and baseline characteristics, descriptive statistics including frequencies, means, medians, range, and cross-tabulation were performed. Differences between two groups (with and without recurrence of VTE) were evaluated using a chi-squared or Fisher's exact test, median test, and *t*-test or Mann-Whitney test when appropriate. Demographic and clinical characteristics of patients with and without recurrence of VTE were descriptively summarized. Since patients' follow-up time differed, incidence rate was estimated. The incidence rate was calculated with a numerator equal to a number of patients who had recurrent episode(s) of VTE during the observational period and a denominator equal to a number of person-years at risk (observed from the date of initial episode until the second event occurred or last day of follow-up). Patients with more than one recurrence were also reported. Additionally, the cumulative proportion of recurrent VTE was estimated using a Nelson-Aalen cumulative hazard estimate method. A second and third recurrent event after the second episode of VTE was not included in the cumulative proportional analyses.

Potential risk factors such as the patient's demographics, baseline and clinical laboratory parameters, chronic medical problems, use of venous catheter, anticoagulation therapy (yes/no), and anticoagulation therapy duration were examined through univariate and multivariate Cox Proportional Hazards models. Hazard ratio (HR) and 95% confidence intervals (CIs) were calculated for each variable. We used backward stepwise Cox Proportional Hazard method to identify a final multivariate Cox model. Initially, any variable with a *p*-value ≤0.25 in the univariate Cox model or log-rank test was required to enter the model. Data on patients without events was censored at the earliest death or May 2010, whichever occurred first. All data analysis were performed using the Stata version 13 (STATA Corp., College Station, TX), and *p*-values <0.05 (2-tailed) were considered statistically significant.

3. Results

Patients who admitted to Leukemia department, MD Anderson Cancer Center for treatment were retrospectively identified through the institution's electronic health record database (Clinic Station). During the period from November 1999 to May 2005, 1295 patients with acute leukemia were identified. Of these patients, 139 patients (86/996 AML and 53/299 ALL) who developed the first VTE were included in the study. Once included, the patients were observed and followed until their death or to end of the study in May 2010, whichever occurred first. Data on the patients were regularly updated. At the time of VTE diagnosis; 94 (67.6%) had active leukemia and 45 (32.4%) had achieved remission. VTE was identified in 4 (2.8%) patients within 1 month prior to leukemia diagnosis, 18 (12.9%) at the time of leukemia diagnosis, 90 (64.8%) within 12 months after leukemia diagnosis, 15 (10.8%) within 12–24 months, and 12 (8.7%) after 24 months of leukemia diagnosis. The mean time to initial VTE event for ALL patients was 1.6 months (median time: 2.4 months) and the mean time to initial VTE event for AML patients was 2 months (median time: 4.5 months). All of these patients, including those with VTE at the time of leukemia diagnosis and those who had VTE development later in the course of their treatment, were entered into the final analysis. The median age of the entire study population was 55 years [inter-quartile range (IQR): 40–65]; 43.2% (60 patients) of the population was female; and 78.4% (109 patients) was Caucasian.

3.1. Patient demographics and baseline characteristics

Twenty seven patients of the total study cohort had recurrent VTE and 112 patients did not develop recurrence (before they died or up to the end of the observational period in May 2010). Of the 27 patients with recurrent VTE, 19 (70.4%) had active leukemia and 8 (29.6%) were in remission at the time of diagnosis. Demographic and clinical characteristics of the patients with and without recurrent VTE are presented in Table 1. Results are presented as absolute frequencies or mean (range, standard deviation). The median follow-up time was 10.7 months (range: 0.13–120.0 months).

In general, the two groups were similar. Patients in non-recurrent groups were slightly older than those in the recurrent VTE group, but this was not significantly different (median age 53.3 years vs. 48 years, $p = 0.14$). The recurrent VTE group had more obese patients, but not significantly more (40.7% vs. 26.8%, $p = 0.50$). Patients in the recurrent VTE group had a larger percentage of secondary leukemia (22.2% vs. 8%, $p = 0.06$). Approximately 31% of patients in both groups did not receive anticoagulation therapy. The mean anticoagulation duration was 1.5 months and 3.2 months, respectively among non-recurrent and recurrent groups. Of the 27 patients with recurrent VTE, 15 (55.6%) received a variation of anticoagulation therapy. Anticoagulation therapy was maintained for >6 months and 3 months in 7 (25.9%) and 10 (37.0%) patients, respectively. There was no difference in recurrence rate based on acute leukemia subtype.

3.2. Thrombotic Events.

Of the 139 adult acute leukemia patients with an initial episode of VTE (86 AML, 53 ALL), 27 patients (19.4%; 16 AML and 11 ALL) experienced one or more documented recurrent episode(s) of VTE. Of the 27