Thrombosis Research 183 (2019) 131–135

Contents lists available at ScienceDirect

Thrombosis Research

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

Full Length Article

Incidence and characteristics of venous thromboembolism in Asian patients with primary central nervous system lymphoma undergoing chemotherapy

Ja Min Byun[a], Junshik Hong[a,*], Sung-Soo Yoon[a], Youngil Koh[a], Chan-Young Ock[a], Tae Min Kim[a], Ji Hyun Lee[b], Sung-Hyun Kim[b], Jeong-Ok Lee[c], Soo-Mee Bang[c], Ho-Young Yhim[d], Sung Hwa Bae[e], Yeung-Chul Mun[f], Doyeun Oh[g], Korean Thrombosis and Hemostasis Working Party of Korean Society of Hematology

[a] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[b] Department of Internal Medicine, Dong-A University of College of Medicine, Busan, Republic of Korea
[c] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[d] Department of Internal Medicine, Chonbuk National University Hospital, Jeonju, Republic of Korea
[e] Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu, Republic of Korea
[f] Department of Internal Medicine, Ewha Women's University School of Medicine, Seoul, Republic of Korea
[g] Department of Internal Medicine, School of Medicine, CHA University, Seongnam, Republic of Korea

ARTICLE INFO

Keywords:
Primary central nervous system lymphoma
Venous thromboembolism
Risk factor
Incidence
Asian

ABSTRACT

Background: Venous thromboembolism (VTE) may lead to diminished quality of life and ultimately worse prognosis in cancer patients, but there is limited data on the incidence, risk factors and mortality impact of VTE in Asian primary central nervous system lymphoma (PCNSL) patients.
Objectives: To report the incidence, risk factors and mortality impact of VTE in Asian PCNSL patients.
Methods: From 7 academic centers in Korea, 235 newly diagnosed PCNSL patients undergoing chemotherapy were retrospectively identified during period of January 2004 to September 2018.
Results: All patients but 12 (6 T-cell, 6 other B-cell) had diffuse large B-cell lymphoma. During the median follow-up of 21 months, 33 patient (14.0%) developed VTE. Of the VTE events, 11 (33.3%) were deep vein thrombosis (DVT), 15 (45.5%) were pulmonary thromboembolism (PTE), and 7 (21.2%) were DVT with PTE. The median time to VTE was 2 months and the one-year actuarial incidence was 11.7%. On multivariate analysis, ECOG performance ≥ 2, age > 60 years, female sex, and Hb < 10 g/dL were independently associated with VTE. The patients with VTE were associated with shorter disease specific survival ($P = 0.046$) and overall survival ($P = 0.022$).
Conclusion: Overall, the incidence of VTE in Asian PCNSL seems to be lower compared to Western population. As VTE development is associated with overall survival and indicative of relapse, careful close monitoring is warranted.

1. Introduction

Venous thromboembolism (VTE) is a serious complication in cancer patients, leading to significantly increased morbidity and mortality [1,2]. Recognized pathogenic mechanisms include paraneoplastic tissue factor secretion, platelet activation, coagulation factor alteration, and endothelial damage [3]. Certain malignancies are associated with a higher incidence of VTE than others, and lymphoma is one of these malignancies [4,5]. The reported VTE incidence in patients with lymphoma ranges from 5 to 17%, with a higher incidence in patients with primary central nervous system lymphoma (PCNSL) [6–9].

However, the majority of these previous studies focused on Caucasian patients, and thus the results cannot be readily extrapolated to Asian populations because the reported incidence of both idiopathic VTE [10] and certain types of cancer-associated VTE [11,12] is lower in Asian populations compared to those of other ethnicities. Interestingly, for patients with lymphoma, the reported incidence of VTE in Asian populations seems to be comparable to that of western populations [13,14]. Unfortunately, the constitution of the study population was heterogeneous in the aforementioned reports, and more importantly,

* Corresponding author.
E-mail address: alertjun@hanmail.net (J. Hong).

https://doi.org/10.1016/j.thromres.2019.10.002
Received 27 June 2019; Received in revised form 27 September 2019; Accepted 8 October 2019
Available online 20 October 2019

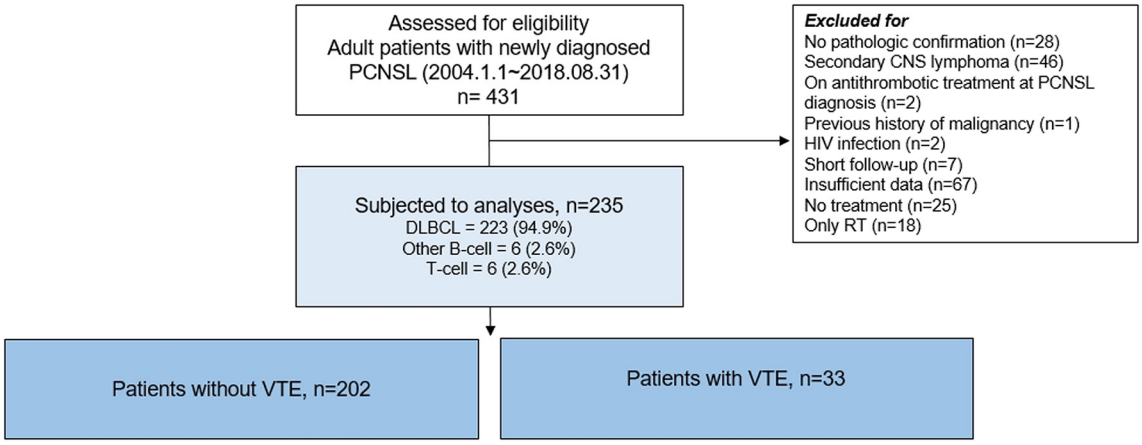

Fig. 1. CONSORT diagram.

only a handful of PCNSL patients were included in the analyses. The incidence, risk factors and mortality impact of VTE in Asian patients with PCNSL remain largely unknown. To this end, we have carried out this study to comprehensively investigate the development of VTE and its effects in a homogeneous Asian population with PCNSL.

2. Methods

2.1. Patients

From 7 academic centers in Korea, 431 newly diagnosed PCNSL patients were retrospectively identified during the period of January 2004 to August 2018. Using the electronic medical records, International Classification of Diseases (ICD-10) codes C859 and C8598 were employed to select the potential patients. Newly diagnosed PCNSL was defined as a pathologically confirmed case in someone without a previous history of lymphoma of any kind. Adult patients, defined as 18 years old or older who received at least one cycle of chemotherapy, were included, while cases without pathologic confirmation, with secondary central nervous system lymphoma, on antithrombotic treatment at the time of PCNSL diagnosis, with a history of other malignancy within 2 years of the PCNSL diagnosis, with a history of HIV infection, and those lost to follow-up within 6 months of diagnosis were excluded. Patients who did not receive chemotherapy and those who only received radiotherapy were also excluded. A hematologist with clinical experience of 5 years or more from each participating center was responsible for data collection. The collected data were then centrally reviewed by 2 independent hematologists for data quality assurance. This study was conducted according to the Declaration of Helsinki and was approved by the institutional review board of all of the participating hospitals.

2.2. Statistical analysis

Differences between groups were assessed using Student's *t*-test or one-way analysis of variance for continuous variables and a Pearson chi-square test for categorical variables, as indicated. The overall survival (OS) and disease-specific (PCNSL-specific) survival curves were estimated using the Kaplan-Meier method. OS was defined as the time from PCNSL diagnosis to death from any cause, while disease-specific survival was defined as the time from PCNSL diagnosis to death from PCSNL. If patients survived without death or progression, survival was censored at the last date of follow-up when no death or progression was confirmed, and data available up to March 2019 were used. The associations between VTE and OS and between VTE and disease-specific survival were analyzed using multivariate Cox proportional hazards regression models. The International Extranodal Lymphoma Study Group (IELSG) prognostic score, based on age, performance status, elevated lactate dehydrogenase, cerebrospinal fluid protein levels and involvement of deep brain structures (periventricular space, basal lymph nodes, cerebellum and brainstem), was used for patient risk stratification [15]. These data were analyzed using the Statistical Package for the Social Sciences software (IBM® SPSS® Statistics, version 22.0).

Gray's test was used to compare the cumulative incidence curves for VTE in the presence of the competing risk of death. Then, multivariable Cox proportional hazards regression models, using the methods of Fine and Gray to adjust for competing risks of death, were used to analyze risk factors associated with VTE. For this part of the analyses, SAS Enterprise Guide 6.1 Version and the statistical software R (www.r-project.org) were used.

P values of < 0.05 were considered statistically significant. A stepwise backward procedure was used to identify independent predictors of each end point. All predictors achieving a *P* value below 0.05 in univariate analyses were considered and were sequentially removed if the *P* value in the multivariate analyses was above 0.05.

3. Results

3.1. Patient characteristics

After excluding 129 patients for meeting the exclusion criteria and an additional 67 patients for missing data, a total of 235 patients were evaluated according to their demographic, laboratory and clinical data (Fig. 1). Table 1 shows the baseline characteristics of the 235 enrolled patients. There were no patients with a previous history of VTE. The median age of the patients was 63 years, and patients with VTE tended to be older than those without VTE (median 67 years vs. 62.5 years, respectively, $P = 0.004$). Generally, patients with VTE had worse disease compared with those without VTE, as evident by a higher proportion of patients classified as high risk by IELSG score (27.3% vs. 7.4%, respectively, $P = 0.001$). Additionally, patients with VTE were associated with a poorer baseline performance compared with those without VTE, as evident by a higher ECOG performance status score ($P < 0.001$) and more patients with impaired ambulation at PCNSL diagnosis (57.6% vs. 34.2%, respectively, $P = 0.010$). When the laboratory findings were considered, patients with VTE had lower hemoglobin (mean 12.2 g/dL ± standard deviation [SD] 1.6 g/dL vs. 13.1 ± 1.5 g/dL, $P = .010$) and lower albumin (mean 3.6 g/dL ± SD 0.2 g/dL vs. 3.8 ± 0.5 g/dL, $P = .015$) compared to those without VTE. There were no differences between the 2 groups with regards to the involved sites and treatment approaches.

Table 1
Baseline characteristics.

Characteristics	Total (N = 235)	VTE (−) (N = 202)	VTE (+) (N = 33)	P
Age, years (median, range)	63 (23–84)	62.5 (23–84)	67 (49–84)	0.004
Age > 60 years (%)	139 (59.1)	115 (56.9)	24 (72.7)	0.087
Sex (male, %)	123 (52.3)	113 (55.9)	10 (30.3)	0.006
BMI at diagnosis (kg/m^2, %)[a]				
< 17.5	12 (5.1)	10 (5.0)	2 (6.1)	0.530
≥17.5– < 23.0	100 (42.6)	83 (41.1)	17 (51.5)	
≥23.0– < 28.0	104 (44.3)	91 (45.0)	13 (39.4)	
≥28.0	19 (8.1)	18 (8.9)	1 (3.0)	
IELSG score (%)				
Low risk (0–1)	71 (30.2)	66 (32.7)	5 (15.2)	0.001
Intermed risk (2–3)	140 (59.6)	121 (59.9)	19 (57.6)	
High risk (4–5)	24 (10.2)	15 (7.4)	9 (27.3)	
ECOG (≥2, %)	117 (50.0)	90 (44.8)	27 (81.8)	< 0.001
Impaired ambulation at dx (%)	88 (37.4)	69 (34.2)	19 (57.6)	0.010
Lymphoma subtype (%)				
DLBCL	223 (94.9)	194 (96.0)	29 (87.9)	0.036
Other B-cell	6 (2.6)	3 (1.5)	3 (9.1)	
T-cell	6 (2.6)	5 (2.5)	1 (3.0)	
Brain parenchymal lesion (%)				
None	14 (6.0)	9 (4.5)	5 (15.2)	0.064
Single	83 (35.3)	70 (34.7)	13 (39.4)	
2–3	95 (40.4)	86 (42.6)	9 (27.3)	
> 4	43 (18.3)	37 (18.3)	6 (18.2)	
Deep brain structure[b] involve (%)	169 (71.9)	143 (70.8)	26 (78.8)	0.343
CSF involvement (%)	174 (74.0)	148 (73.3)	26 (78.8)	0.145
Elevated CSF protein (%)	144 (61.3)	120 (59.4)	24 (72.7)	0.502
Laboratory findings (%)				
Hb < 10 g/dL	6 (2.6)	3 (1.5)	3 (9.1)	0.010
WBC > 11 × 10^9/L	85 (36.3)	75 (37.3)	10 (30.3)	0.438
Platelet ≥350 × 10^9/L	10 (4.3)	8 (4.0)	2 (6.1)	0.584
Elevated LDH	74 (37.2)	60 (35.1)	14 (50.0)	0.130
Albumin < 4 g/dL	164 (69.8)	135 (66.8)	29 (87.9)	0.015
PCNSL treatment (%)				
HD-MTX[c] use	215 (91.5)	187 (92.6)	28 (84.8)	0.190
Rituximab use	131 (55.7)	113 (55.9)	18 (54.5)	0.881
Upfront autoSCT	13 (5.5)	13 (6.4)	0	0.319
RT	137 (58.3)	119 (58.9)	18 (54.5)	0.637

VTE, venous thromboembolism; BMI, body mass index; IELSG score, International Extranodal Lymphoma Study Group score; Intermed, intermediate; ECOG, Eastern Cooperative Oncology Group performance status; dx, diagnosis; DLBCL, diffuse large B-cell lymphoma; CSF, cerebrospinal fluid; Hb, hemoglobin; WBC, white blood cell count; LDH, lactate dehydrogenase; PCNSL, primary central nervous system lymphoma; HD-MTX, high dose methotrexate; autoSCT, autologous stem cell transplantation.

[a] Asia-Pacific classification of BMI was used.

[b] Deep structure included periventricular lesions, basal ganglia, corpus callosum, brain stem, or cerebellum.

[c] HD-MTX refers to methotrexate dose equivalent to or > 3 g/m^2.

3.2. Incidence and manifestations of VTE

During the median follow-up of 21 months, 33 patients (14.0%) developed VTE. Among these cases, 21 cases (21/33, 63.6%) occurred within 6 months of the PCNSL diagnosis (Fig. 2). Of the VTE events, 11 (33.3%) were deep vein thrombosis (DVT), 15 (45.5%) were pulmonary thromboembolism (PE), and 7 (21.2%) were DVT with PE. All of the 11 DVT cases showed symptoms associated with VTE: 2 patients complained of pain, and 9 patients complained of swollen limbs. All of the 15 PE cases were associated with dyspnea. Among the 7 DVT with PE cases, 2 patients had symptoms associated with DVT, and 5 patients had symptoms associated with PE. All but 1 case of PE were objectively confirmed by either computed tomography (CT) or ultrasonography. None of the VTE events were catheter-associated. The median time

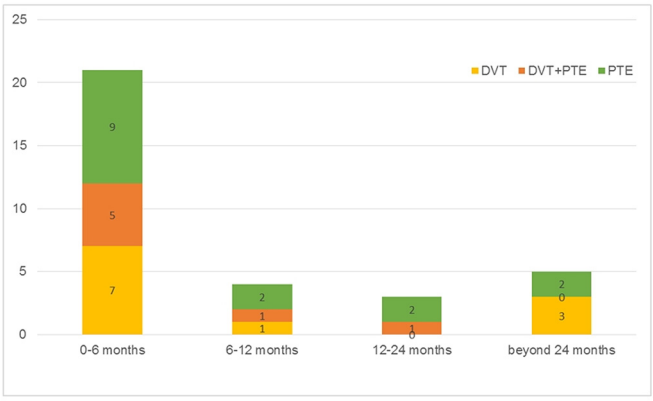

Fig. 2. The clinical patterns and onset of venous thromboembolism events.

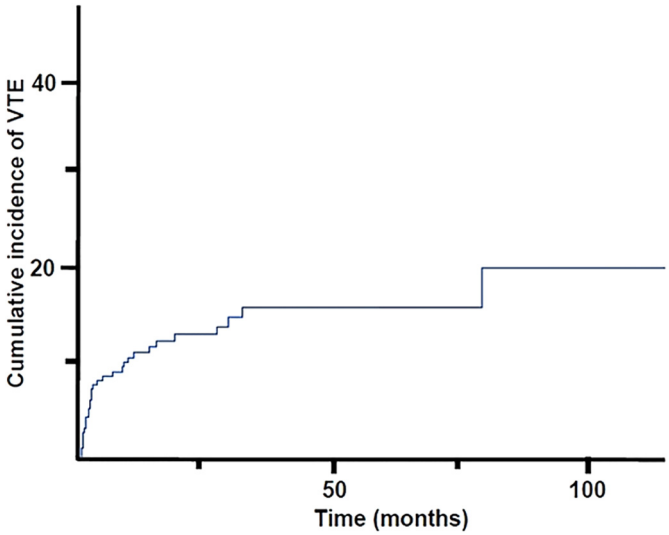

Fig. 3. The cumulative incidence of venous thromboembolism.

between PCNSL diagnosis to VTE occurrence was 2 months, and the 3-, 12- and 24-month cumulative incidences of VTE were 8.2% (95% CI 5.11–12.18), 11.7% (95% CI 7.87–16.37), and 13.9% (95% CI 9.51–19.20), respectively (Fig. 3). A VTE occurrence beyond 24 months from PCNSL diagnosis was associated with relapse in all 5 cases. All patients except 2 had active disease when VTE occurred.

For treatment of the VTE, 31 patients initially received low-molecular-weight heparin (LMWH). Among these 31 patients, 7 patients switched to warfarin, 5 switched to direct oral anticoagulants (DOAC), and 19 patients continued with LMWH. A total of 5 (16.1%) major bleeding incidences were noted: 1 in the form of gastrointestinal bleeding requiring intervention in a DOAC user, and 4 as unspecified bleeding causing a decrease in hemoglobin levels of 2 g/dL or more in LMWH users. The latter patients did not require intervention for bleeding control but did receive a transfusion. For the 2 patients who did not receive any coagulation, one patient underwent inferior vena cava (IVC) filter insertion, while the other patient presented to the emergency department as death-on-arrival due to a fatal PE and, thus, no treatment was necessary. No patients required thrombolysis.

3.3. Risk factors for VTE

The age at diagnosis, ECOG performance status, female sex, impaired ambulation at diagnosis, hypoalbuminemia (albumin < 4 g/dL), and anemia (Hb < 10 g/dL) were associated with VTE development in the univariate analysis. On multivariate analysis, age > 60 years old,

Table 2
Competing risk factor analysis for VTE development.

	Hazard ratio	95% confidential interval	*P*
Female sex	2.344	1.099–4.998	0.027
Age > 60 years	3.259	1.322–8.035	0.010
ECOG ≥2	3.689	1.438–9.460	0.007
Hb < 10 g/dL	3.261	0.895–11.878	0.033

ECOG, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin.

Table 3
The multivariate COX regression for survival.

	Overall survival		Disease-specific survival	
	HR (95% CI)	*P*	HR (95% CI)	*P*
VTE Yes vs. No	2.13 (1.01–4.48)	0.047	1.98 (0.90–4.35)	0.088
Age (years) > 60 vs. ≤60	4.70 (2.06–10.71)	< 0.001	5.24 (2.17–12.67)	< 0.001

HR = hazard ratio; CI = confidence interval; VTE, venous thromboembolism.

ECOG performance status ≥2, female sex and Hb < 10 g/dL were independently associated with VTE (Table 2). Radiation, type and dose of chemotherapeutic agents, body mass index, number of brain parenchymal lesions, platelet count at diagnosis, and WBC count at diagnosis were not associated with VTE development.

3.4. Impact of VTE on survival

Overall, there was 1 VTE-related death. As shown in Table 3, for the OS models, VTE was associated with a significantly increased risk of death (HR 2.22, 95% CI 1.01–4.48, $P = 0.047$). When PCNSL-specific survival was considered, VTE still showed trends towards an increased risk of death (HR 1.98, 95% CI 0.90–4.35, $P = 0.088$).

4. Discussion

One of the strengths of our study is the homogeneity and the size of the study population: a total of 235 Korean patients with PCNSL undergoing chemotherapy were included in the analysis. It has been reported that most VTE develops early in the course of disease in association with chemotherapy [5,13,16–18], which is comparable to our results. On the other hand, although a direct comparison is not possible, the absolute percentage and cumulative incidence seems lower in our cohort compared to those in previous studies that primarily included non-Asian patients [8,16–18]. The highest reported rate of VTE in PCNSL undergoing treatment is 59.5% [8], but that study was conducted mainly in the 1990s with only 25 patients. With vast improvements in supportive care schemes and treatment strategies in PCNSL since the 1990s, the reported VTE rate has decreased to approximately 30%, according to more recent studies [16,17]. In comparison, in our cohort, only 14% of the patients developed VTE, despite having received at least one cycle of chemotherapy. Considering the fact that chemotherapy itself is a well-known risk factor for VTE [19,20], our results suggest that Asian PCNSL patients are in fact less prone to developing VTE compared to non-Asian patients. The rates and cumulative incidence of VTE in our cohort were comparable to a previous Korean study [14]. Our results are further supported by Mahajan et al. [18], who reported Asian/Pacific islanders were at a decreased risk of VTE development compared to non-Hispanic whites (HR = 0.37, 95% CI 0.21–0.66).

In the scope of risk factors for VTE, we found that the treatment modalities did not affect VTE development. As shown in Table 1, most patients received high dose methotrexate based treatment, and there were no significant differences with regards to treatment between patients who developed VTE versus those who did not develop VTE. Instead, female sex, poor ECOG performance status, older age and lower hemoglobin per the Khorana Risk Score for VTE in cancer patients (KRS) were identified as risk factors for VTE. Regarding lower hemoglobin and its impact on VTE development, many studies have already noted the limitations of the KRS in discerning lymphoma patients at higher risk of VTE [21,22]. Especially for Asian patients who rarely have a BMI over 35 kg/m^2, the unmet need for a better VTE assessment model seems more imperative. Nevertheless, lower hemoglobin seems to be a consistent risk factor for VTE in both our study and previous reports [21], and thus watchful follow-up is warranted for this subset of patients.

The impact of VTE on survival remains somewhat controversial. While some reported specific types of VTE (i.e., PE) are associated with an increased risk of death [17], others have reported VTE does not have a negative impact on the OS [14]. In our study, we found that patients with VTE had a significantly shorter OS compared to those without VTE, but VTE was not a prognostic factor on multivariate analysis. A paucity of data precludes us from drawing affirmative conclusions, especially because there was only 1 VTE-related death in our cohort, but it seems that VTE has at least a tentative role as a prognostic indicator. Additionally, it should be noted that VTE development beyond 24 months was largely due to relapse of PCNSL. Taken together, attending physicians should be aware of the significance of VTE development in these patients, closely monitor the patients for signs and symptoms of VTE, and initiate timely interventions when necessary. Briefly, the treatment of VTE was well-tolerated in our cohort. The majority of the patients were treated only with anticoagulation, and bleeding events were noted in 1 of the 5 DOAC users and in 4 of the 19 LMWH users. There were no brain hemorrhages.

The limitations of this study are mostly due to the retrospective nature of the analyses and the short follow-up duration. First, not all patients were tested for inherited thrombophilia. However, for those who developed VTE, serum antithrombin activity, protein C activity, and protein S antigen were measured, and none of these patients had any underlying thrombophilic conditions. Second, while we used statistical methods to adjust for possible confounding, there may be residual confounding. Last, there is a chance that the incidence of VTE was underestimated as (1) patients lost to follow-up within 6 months of diagnosis have been excluded, and (2) asymptomatic VTE might have gone undetected.

Here, we provide a detailed report of the incidence and characteristics of VTE in PCNSL from a large homogeneous population undergoing chemotherapy. The VTE incidence is lower in Asian PCNSL patients compared to non-Asian patients, but the rate is still significantly high; therefore, identifying patients who would benefit from prophylactic anticoagulation seems to be the next step. As VTE development in PCNSL is associated with reduced survival and a possibility of relapse, close monitoring is warranted.

Acknowledgements

The abstract of this manuscript has been presented as a poster at the XXVII Congress of the International Society on Thrombosis and Haemostasis 2019, Melbourne, Australia. We would like to extend our sincere gratitude and appreciation to Ju Hyun Lee of Seoul National University Bundang Hospital for the statistical consultation.

Author contributions

Designed the study: all of the authors. Patient enrollment and data collection: all of the authors. Analyzed the data: Ja Min Byun, Junshik Hong. Wrote the paper: Ja Min Byun, Junshik Hong. Revised the paper: all of the authors.

Declaration of competing interest

No conflicts of interest to disclose.

References

[1] H.T. Sorensen, L. Mellemkjaer, J.H. Olsen, J.A. Baron, Prognosis of cancers associated with venous thromboembolism, N Engl J Med. 343 (25) (2000) 1846–1850.

[2] A.A. Khorana, C.W. Francis, E. Culakova, N.M. Kuderer, G.H. Lyman, Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy, J Thromb Haemost. 5 (3) (2007) 632–634.

[3] G.Y. Lip, B.S. Chin, A.D. Blann, Cancer and the prothrombotic state, Lancet Oncol. 3 (1) (2002) 27–34.

[4] A.A. Khorana, N.M. Kuderer, E. Culakova, G.H. Lyman, C.W. Francis, Development and validation of a predictive model for chemotherapy-associated thrombosis, Blood. 111 (10) (2008) 4902–4907.

[5] K.M. Sanfilippo, T.F. Wang, B.F. Gage, S. Luo, P. Riedell, K.R. Carson, Incidence of venous thromboembolism in patients with non-Hodgkin lymphoma, Thromb Res. 143 (2016) 86–90.

[6] V. Caruso, A. Di Castelnuovo, S. Meschengieser, M.A. Lazzari, G. de Gaetano, S. Storti, et al., Thrombotic complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18,018 patients and 1149 events, Blood. 115 (26) (2010) 5322–5328.

[7] M. Mohren, I. Markmann, K. Jentsch-Ullrich, M. Koenigsmann, G. Lutze, A. Franke, Increased risk of thromboembolism in patients with malignant lymphoma: a single-centre analysis, Br J Cancer. 92 (8) (2005) 1349–1351.

[8] N. Goldschmidt, E. Linetsky, E. Shalom, D. Varon, T. Siegal, High incidence of thromboembolism in patients with central nervous system lymphoma, Cancer. 98 (6) (2003) 1239–1242.

[9] R.S. Komrokji, N.P. Uppal, A.A. Khorana, G.H. Lyman, K.L. Kaplan, R.I. Fisher, et al., Venous thromboembolism in patients with diffuse large B-cell lymphoma, Leuk Lymphoma. 47 (6) (2006) 1029–1033.

[10] J. Hong, J.H. Lee, H.Y. Yhim, W.I. Choi, S.M. Bang, H. Lee, et al., Incidence of venous thromboembolism in Korea from 2009 to 2013, PLoS One. 13 (1) (2018) e0191897.

[11] Y. Koh, S.M. Bang, J.H. Lee, H.J. Yoon, Y.R. Do, H.M. Ryoo, et al., Low incidence of clinically apparent thromboembolism in Korean patients with multiple myeloma treated with thalidomide, Ann Hematol. 89 (2) (2010) 201–206.

[12] S.Y. Oh, J.H. Kim, K.W. Lee, S.M. Bang, J.H. Hwang, D. Oh, et al., Venous thromboembolism in patients with pancreatic adenocarcinoma: lower incidence in Asian ethnicity, Thromb Res. 122 (4) (2008) 485–490.

[13] K. Yokoyama, M. Murata, Y. Ikeda, S. Okamoto, Incidence and risk factors for developing venous thromboembolism in Japanese with diffuse large b-cell lymphoma, Thromb Res. 130 (1) (2012) 7–11.

[14] L.C. Park, S.Y. Woo, S. Kim, H. Jeon, Y.H. Ko, S.J. Kim, et al., Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: results from a prospective cohort study with Asian population, Thromb Res. 130 (3) (2012) e6–12.

[15] A.J. Ferreri, J.Y. Blay, M. Reni, F. Pasini, M. Spina, A. Ambrosetti, et al., Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience, J Clin Oncol. 21 (2) (2003) 266–272.

[16] S. Hohaus, M.C. Tisi, F. Bartolomei, A. Cuccaro, E. Maiolo, E. Alma, et al., Risk factors for venous thromboembolism in patients with lymphoma requiring hospitalization. Blood, Cancer J. 8 (6) (2018) 54.

[17] B.C. Gayathri Ravi, Erica L. Campagnaro, Basem M. William, Richard J. Creger, Stanton L. Gerson, Marcos De Lima, Hillard M. Lazarus, Paolo Caimi, Increased risk of venous thromboembolism in primary central nervous system lymphoma patients undergoing therapy, Blood. 124 (2014) 5421.

[18] A.M.B. Anjlee Mahajan, Theresa H.M. Keegan, Aaron S. Rosenberg, Ted Wun, Increased risk of venous thromboembolism in primary central nervous system lymphoma patients undergoing therapy, Blood. 130 (2017) 754.

[19] J.W. Blom, J.P. Vanderschoot, M.J. Oostindier, S. Osanto, F.J. van der Meer, F.R. Rosendaal, Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study, J Thromb Haemost. 4 (3) (2006) 529–535.

[20] G.H. Lyman, L. Eckert, Y. Wang, H. Wang, A. Cohen, Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis, Oncologist. 18 (12) (2013) 1321–1329.

[21] J. Rupa-Matysek, L. Gil, M. Kazmierczak, M. Baranska, M. Komarnicki, Prediction of venous thromboembolism in newly diagnosed patients treated for lymphoid malignancies: validation of the Khorana Risk Score, Med Oncol. 35 (1) (2017) 5.

[22] D. Antic, N. Milic, S. Nikolovski, M. Todorovic, J. Bila, P. Djurdjevic, et al., Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients, Am J Hematol. 91 (10) (2016) 1014–1019.