

ORIGINAL ARTICLE



Venous thromboembolism in primary central nervous system lymphoma during frontline chemoimmunotherapy

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Abstract

Background: In primary central nervous system lymphoma (PCNSL), venous thromboembolism (VTE) can cause significant morbidity and hinder chemotherapy delivery. **Objectives:** To assess VTE incidence, timing and adequacy of inpatient and outpatient VTE prophylaxis in patients with PCNSL receiving chemoimmunotherapy with curative intent.

Patients/Methods: We reviewed patients diagnosed with PCNSL between 1997 and 2018 who received methotrexate, procarbazine, and vincristine $\pm$ Rituximab. Patient demographics, VTE prophylaxis and incidence, adverse events of anticoagulation, and survival outcomes were collected.

Results: Fifty-one PCNSL patients were included (median 67 years [range, 32-87], 30 males [59%]). Thirteen patients (25%, 95% confidence interval [CI], 14-40) developed VTE at a median of 1.6 months from diagnosis (range, 0-4). Patients with Khorana Risk Score ≥ 2 were more likely to have VTE than those with a KRS < 2 (60% vs 15%; $P = .01$). Eighty-five percent had deviations from inpatient VTE prophylaxis guidelines, and outpatient prophylaxis was not routinely administered. Three patients required inferior vena cava filters. Hemorrhagic complications of anticoagulation included an intracranial hemorrhage from therapeutic anticoagulation and three cases of major bleeding from prophylactic anticoagulation. No patients died from VTE or its treatment.

Conclusions: Patients with newly diagnosed PCNSL are at high risk of VTE. Further research is required into optimal VTE prophylaxis in PCNSL.

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KEYWORDS

chemotherapy, deep vein thrombosis (DVT), Khorana Risk Score (KRS), primary central nervous system lymphoma (PCNSL), pulmonary embolism, venous thromboembolism (VTE)

Essentials

- Venous thromboembolism (VTE) frequently complicates the management of lymphomas.
- We conducted a retrospective review on VTE in primary central nervous system lymphoma (PCNSL).
- PCNSL confers a high risk for VTE, especially in the initial diagnostic and chemotherapy period.
- Further research is required in VTE prophylaxis in PCNSL.

1 | INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal lymphoma, comprising approximately 4% of newly diagnosed central nervous system (CNS) tumors with an incidence of 0.47 per 100 000 person-years.¹ Treatment advances in PCNSL have included methotrexate, procarbazine, and vincristine $\pm$ rituximab (R-MPV) chemotherapy²⁻⁵ and the use of high-dose methotrexate (HD-MTX) in combination with radiotherapy.^{6,7}

Venous thromboembolism (VTE) frequently complicates lymphoma treatment.^{8,9} Important factors in pathogenesis for PCNSL likely include physical immobility due to CNS lesions and known VTE risk factors such as obesity, surgery, chemotherapy, and hospitalization.¹⁰ Patients with PCNSL frequently require a long-term central venous access device (CVAD) to facilitate administration of chemotherapy, which may be associated with catheter-associated upper-limb thrombosis (CAVTE). R-MPV may also contribute to thrombosis via multiple pathways including methotrexate leading to elevated homocysteine levels¹¹ and steroids impairing fibrinolysis.¹² Furthermore, R-MPV requires frequent readmission and hospitalization for each cycle of methotrexate administration and supportive care until clearance. In this situation, it is not known whether outpatient VTE prophylaxis is beneficial. The occurrence of VTE can cause significant morbidity and impact chemotherapy delivery and rehabilitation through complications of VTE. There is a higher risk of intracranial hemorrhage (ICH) while on anticoagulation,¹³ a concern for PCNSL due to the lymphoma location and the timing of anticoagulation in relation to diagnostic surgical procedures.

No predictive scoring tool is available to assess individual risk of VTE in this population. The Khorana Risk Score (KRS) has been used to identify patients at high risk of VTE in solid cancers¹⁴ and has recently been validated in lymphoma¹⁵ but not specifically PCNSL. To date, there have been limited studies describing the incidence of VTE in patients with PCNSL in the HD-MTX era.¹⁶⁻¹⁸ Hence, we investigated VTE incidence, risk factors, and outcomes in a cohort of 51 patients receiving chemoimmunotherapy with curative intent.

2 | METHOD

Fifty-one consecutive patients with newly diagnosed PCNSL between 1997 and 2018 and treated with initial curative intent with R-MPV chemotherapy were identified from a lymphoma database. The diagnosis of PCNSL was based on contemporaneous WHO classification, and only high-grade PCNSL was included. This database was retrospectively annotated from 1997 to 2013 and prospectively curated from 2013 to 2018 based on patients from a single tertiary hospital with cross reference to medical records and medical imaging. Only adult patients who received at least one cycle of R-MPV were included. No other exclusion criteria were applied. R-MPV chemotherapy was administered for five cycles, with a further two cycles administered to patients who do not achieve complete remission.¹⁹ This response was consolidated with two cycles of cytarabine. Patients aged younger than 60 years also received 30.6 Gy of whole-brain radiation therapy before cytarabine consolidation.

Information on all patient demographics, VTE prophylaxis, and overall survival (OS) were obtained from medical records. A VTE event was recorded if it was confirmed radiologically and occurred between 14 days before PCNSL diagnosis and 30 days following completion of chemo/radiotherapy. We defined VTE as pulmonary embolism (PE), lower-limb deep vein thrombosis (LLDVT) in the proximal or distal systems and upper-extremity VTE including CAVTE affecting the deep systems (brachial or more proximal veins). Imaging criteria for PE were a new intraluminal filling defect on subsegmental or more proximal branches on computed tomography (CT) pulmonary angiography or new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy on two views. Similarly, LLDVT radiological confirmation criteria was defined as a new noncompressible venous segment on ultrasonography. CAVTE radiology criteria were new noncompressibility of a venous segment of the upper extremity (including internal jugular), absent or reduced flow on Doppler with no effect from respiration or compression of the arm, or presence of echogenic material on ultrasound or intraluminal filling defect in a venous segment of the arm on venography, CT, or magnetic resonance imaging. Additional information collected

for the VTE cohort included mode of anticoagulation and anticoagulation-related adverse events.

Primary end points of the study were VTE incidence and timing and adequacy of inpatient prophylaxis and outpatient VTE prophylaxis. Surveillance for VTE was not routinely performed. Secondary outcomes included anticoagulation- and VTE-related adverse events (AEs), impact on overall survival, inferior vena cava (IVC) filter usage and whether the KRS or International Extranodal Lymphoma Study Group prognostic score²⁰ is associated with VTE development. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, and bleeding was assessed using ISTH definitions.^{21,22} Adequacy of inpatient VTE prophylaxis was assessed for every hospital admission while the prescription of outpatient VTE prophylaxis was recorded. Inpatient VTE prophylaxis evaluation was based on a qualitative assessment tool validated in surgical patients where "complete" prophylaxis is initiation of anticoagulation within 24 hours of admission without interruptions, "delayed" where prophylaxis is started at >24 hours with no interruptions and "interrupted" if there is omission of VTE prophylaxis for >24 hours.²³ We also assessed the use of nonpharmacologic prophylaxis such as graduated or intermittent pneumatic compression stockings in patients who had a contraindication to prophylactic dose anticoagulation.

Overall survival and time-to-event analyses were calculated from date of diagnosis to death or progression and analyzed by Kaplan-Meier estimation. Comparison between cohorts was undertaken via the Mantel-Haenszel approach to compute a hazard ratio (HR). Differences in proportions were tested using Fisher's test and differences in means of continuous variables were tested using the t test. Significance was set at $P < .05$. Statistical analysis was performed using Prism version 7.0e (GraphPad Software, La Jolla, CA, USA). This study was approved by the local institution ethics committee.

3 | RESULTS

In the 51 patients with newly diagnosed PCNSL who received R-MPV, the median follow-up was 27 months (range, 1-153). All patients had peripherally inserted central catheters (PICCs) for venous access. Table 1 shows patient and disease characteristics comparing patients who developed VTE versus those who did not. Median age at diagnosis was 66.6 years (range, 31.8-86.7), with 61% of patients being >60 years old. No patients had a prior solid-organ transplant or diagnosis of lymphoma. One patient had HIV infection. Only one patient who was on an antiplatelet agent upon PCNSL diagnosis remained on this throughout all cycles of chemotherapy. Three other patients were on aspirin but this was stopped upon PCNSL diagnosis.

Thirteen patients developed VTE (25%; 95% confidence interval [CI], 14-40; four proximal and one distal lower-limb DVTs, one isolated PE, three with a combination of DVT and PE, and four CAVTE affecting the axillary vein) at a median of 1.6 months (range, 0-4) from diagnosis (Figure 1). Eighty-six percent of patients who developed VTE were symptomatic at the time of diagnosis, with one

TABLE 1 Patient characteristics PCNSL with VTE versus no VTE

Characteristic	Developed VTE N = 13 N (%)	Did not develop VTE N = 38 N (%)
Male*	4 (31)	26 (68)
Age, y, median (range)	70.3 (57.4-86.7)	60.0 (31.8-83.1)
>60 y old	12 (92)	19 (50)
ECOG > 1	6 (46)	13 (34)
Presenting hemoglobin, g/L (mean, 95% CI)*	115 (69.9-160.1)	139 (103.5-174.2)
Hemoglobin < 10 g/L and/or ESA use*	4 (31)	1 (3)
Prechemotherapy platelet count $\geq 350 \times 10^9/L$	0 (0)	1 (3)
Prechemotherapy leukocyte count $> 11 \times 10^9/L$	1 (8)	9 (24)
BMI > 35 kg/m ²	3 (23)	0 (0)
BMI, kg/m ² (mean, 95% CI)*	29.6 (17.2-42.0)	24.3 (16.3-32.3)
Elevated LDH, U/L	3 (23)	13 (34)
Elevated CSF protein concentration, g/L	11 (85)	33 (87)
Involvement of deep regions of brain	8 (62)	21 (55)
IELSG prognostic score		
Low	1 (8)	6 (16)
Intermediate	7 (54)	25 (66)
High	5 (38)	7 (18)
Khorana Risk Score*		
1	4 (31)	22 (79)
≥ 2	9 (69)	6 (21)
VTE prophylaxis		
Full	2 (16)	1 (5)
Delayed	2 (16)	9 (43)
Interrupted	6 (50)	18 (86)
Mechanical only	0 (0)	1 (5)
None	2 (16)	1 (5)

Abbreviations: BMI, body mass index; CI, confidence interval; CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group; ESA, erythropoietin stimulating agent; IELSG, International Extranodal Lymphoma Study Group; LDH, lactate dehydrogenase; VTE, venous thromboembolism.

* $P < .05$.

incidental diagnosis in the setting of suspected heparin-induced thrombocytopenia. Fifty-seven percent who developed VTE in our cohort were diagnosed as an outpatient, in between cycles of R-MPV (three LLDVT and four CAVTE). Those diagnosed with VTE were older with a median age of 70 years (range, 57.4-86.7) compared to 60 years (range, 31.8-83.1) in the non-VTE group ($P = .006$) and were more likely to be female (69% versus 32%; $P = .02$). Mean

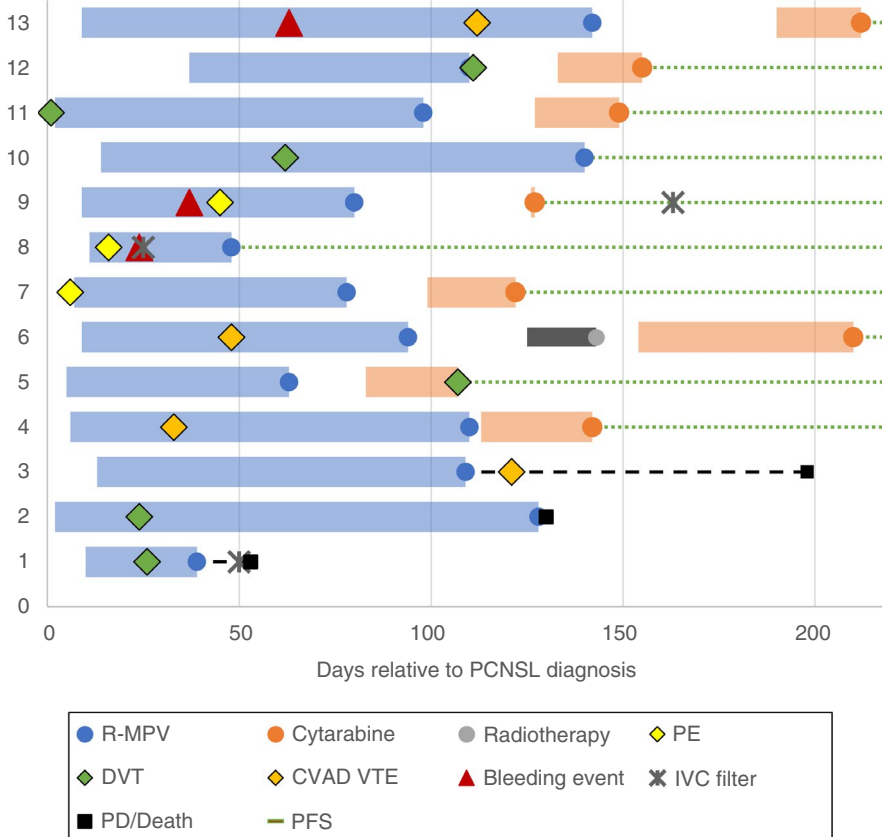


FIGURE 1 PCNSL cases with VTE. CVAD, central venous access device; DVT, deep vein thrombosis; IVC, inferior vena cava; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PE, pulmonary embolism; PFS, progression free survival; R-MPV, methotrexate, procarbazine, and vincristine $\pm$ rituximab; VTE, venous thromboembolism

presenting hemoglobin was lower at 115 g/L (95% CI, 69.9-160.1) compared to 139 g/L (95% CI, 103.5-174.2) in the non-VTE group ($P = .002$). The VTE group also had a higher mean body mass index (BMI), 29.6 kg/m² (95% CI, 17.2-42.0) versus 24.3 kg/m² (95% CI, 16.3-32.3; $P = .002$). Patients with KRS ≥ 2 were more likely to have VTE than those with a KRS < 2 (60% vs 15%; $P = .01$). Other characteristics listed in Table 1 were similar between the two groups. The duration of first hospitalization was similar between the VTE and non-VTE group (median, 36 [range, 5-199] vs 23 days [range, 3-216]; $P = .88$) as was the number of admissions (median, 5 [range, 1-17] vs 9 [range, 1-18]; $P = .16$).

Inpatient VTE prophylaxis comprised chemical (enoxaparin 40 mg daily or heparin 5000 IU twice daily), graduated compression stockings, or concurrent warfarinization for secondary stroke prophylaxis in 85%, 6%, and 3%, respectively. Only one patient on warfarin received outpatient anticoagulation before being diagnosed with VTE and switched to rivaroxaban. In patients diagnosed with VTE, nearly all VTE prophylaxis was incomplete due to delayed initiation (16%), interruptions (50%) or none being prescribed (16%). In the patients with no prophylaxis, one was intentionally withheld due to active gastrointestinal bleeding. One patient of the 16% who had complete prophylaxis received this due to being on warfarin for secondary stroke prophylaxis. In the rest of the patients without VTE, inpatient VTE prophylaxis was similarly incomplete (Table 1). While on VTE prophylaxis, there were three major bleeding events, including a rectus sheath hematoma and two episodes of gastrointestinal bleeding.

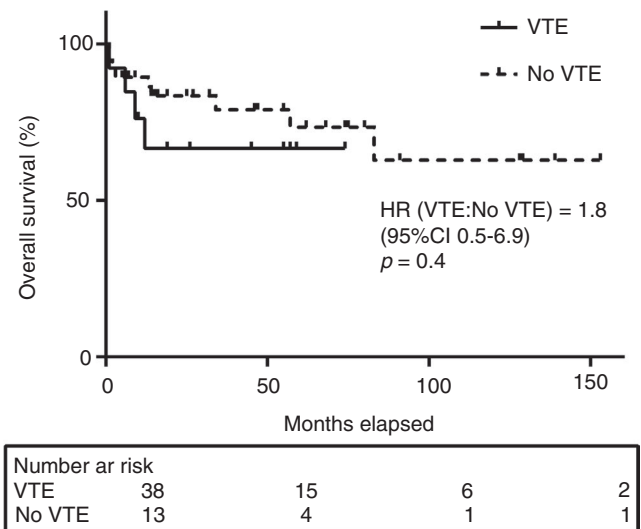


FIGURE 2 Overall survival in PCNSL: VTE versus no VTE. HR, hazard ratio; PCNSL, primary central nervous system lymphoma; VTE, venous thromboembolism

On VTE diagnosis, therapeutic anticoagulation was started within a median of 4 hours. Initial anticoagulation consisted of low-molecular-weight heparin (LMWH; 77%) and intravenous unfractionated heparin (UFH; 23%) while maintenance consisted of LMWH (69%), direct oral anticoagulants (DOACs; rivaroxaban, 23%) and warfarin (8%). Three patients required IVC filters, one prophylactically in the perioperative setting, another due to grade 2 ICH after

anticoagulation, and the third due to the suspicion of ICH, which did not eventuate. There was no other major bleeding from therapeutic anticoagulation. All patients with CAVTE had their PICC removed. In 75%, the PICC was removed after CAVTE diagnosis despite the PICC retaining function with no suspicion of infective complications. No patients had VTE extension or recurrence and none died from VTE or its treatment. There was no difference in OS between the patients who developed VTE and those who did not (Figure 2, HR [VTE:No VTE] = 1.8; 95% CI, 0.5-6.9; $P = .4$).

4 | DISCUSSION

The VTE incidence in PCNSL was 25%, with new events being most frequent during the initial diagnostic and chemotherapy period. This is congruent with previous research supporting the association between diffuse large B-cell lymphoma (DLBCL) and an increased risk of VTE.^{8,9} Risk factors for VTE in DLBCL were found to be chemotherapy, prior history of VTE, and obesity.⁸ A large retrospective review identified a HR of 1.74 of VTE in patients with DLBCL compared to follicular lymphoma.⁸ This cohort specifically excluded PCNSL, and it is therefore difficult to extrapolate these results to our population. Similar to our results, however, their median time to VTE was 2 months.

Another review of 54 patients with PCNSL treated with methotrexate-based regimens and osmotic blood-brain barrier disruption had a much higher VTE incidence of nearly 60% and associated mortality of 7%.¹⁶ The reason for the marked difference in outcomes could be partly attributable to their reduced rate of VTE prophylaxis. Two retrospective reviews of patients with PCNSL treated with HD-MTX-based regimens who received routine inpatient prophylactic anticoagulation found a similar VTE incidence to our observed rates, and VTE episodes all occurred within two cycles of HD-MTX chemotherapy.^{17,18}

As in previous studies, KRS was found to predict risk of VTE in lymphoma,¹⁵ and we hypothesized that it could also be useful in PCNSL. Adjustment of risk categories, labeling $KRS \geq 2$ as "high risk" rather than $KRS \geq 3$, may be required. In the initial KRS study, there were limited patients with brain tumors or poor performance status, and therefore it is not surprising that this tool needs to be adapted to our population. PCNSL confers an at least intermediate risk ($KRS \geq 1$) secondary to cancer type. While our VTE group had a higher BMI and lower presenting hemoglobin than the non-VTE group, prechemotherapy leukocyte and platelet counts were similar between the two groups. In addition, our VTE group was older and had more females. While modification of KRS specifically for PCNSL would be ideal, practically this would be difficult given the relative rarity of this disease.

Given the high rate of early VTE, optimal VTE prophylaxis in this setting requires further research. In our study, we had no ICH from prophylactic LMWH, which was withheld appropriately perioperatively. This practice is also supported by previous studies in patients undergoing neurosurgical interventions.²⁴ Most

incidents of interrupted prophylaxis were to facilitate stereotactic biopsy of the CNS lesion and were therefore unavoidable as routine prophylaxis was administered at 2000 hours. The use of mechanical prophylaxis to bridge the anticoagulation-free period was not widely employed, highlighting an area of potential improvement. Our institution has recently changed routine administration of VTE prophylaxis to 1600 hours, thereby abolishing the need to withhold the dose the day before planned procedures. Our assessment of inpatient VTE prophylaxis has limitations, as there are no other validated scoring systems apart from that which we used. This scoring system has been applied to surgical patients and remains applicable to our cohort of postoperative patients who all had neurosurgical procedures.

Our VTE event rate raises the possibility that current VTE prophylaxis regimens are inadequate for PCNSL. Fifty-seven percent who developed VTE in our cohort were diagnosed as an outpatient in between cycles of R-MPV. In this cohort, 43% developed LLDVT and/or PE and all these patients had $KRS \geq 2$. While we concede that incomplete inpatient VTE prophylaxis could have led to the high rate of VTE diagnosed in between admissions, the role of chemical outpatient VTE prophylaxis is worth further exploration.

Previously, the risk-benefit ratio was against routine outpatient VTE prophylaxis in cancer, partly due to the injection burden of LMWH.²⁵ Recent trials on thromboprophylaxis have focused on high-risk ambulatory patients with cancer (defined as $KRS \geq 2$) using rivaroxaban or apixaban for prophylaxis.^{26,27} The generalizability to our PCNSL cohort is unclear, as patients were excluded if they had a primary brain tumor or brain metastases in the CASSINI (A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism [VTE] Prophylaxis in Ambulatory Cancer Participants) trial while the apixaban study included only 4.2% brain cancer. In addition, the majority of VTE diagnoses in the outpatient setting for our cohort were CAVTE. In the prevention of CAVTE in cancer, the administration of LMWH is of unclear benefit,²⁸⁻³¹ while limited evidence is available for DOACs.^{32,33}

In our study, there were no VTE-related deaths. The development of VTE did not seem to be associated with decreased overall survival; however, our study was insufficiently powered. Our findings could also partially be due to the inclusion of CAVTE, which was excluded from previous studies.^{9,14,34,35}

Nearly one-third of our VTEs were PICC-related CAVTE. Most patients had their PICC removed upon CAVTE diagnosis. This is surprising given that multiple international guidelines have suggested catheter maintenance in the absence of malposition, malfunction, or implication in sepsis.²⁸⁻³¹ Given our findings, consideration for other central venous catheters rather than PICCs should be considered as the latter confers a higher risk of VTE (odds ratio, 2.55; 95% CI, 1.5-4.2; $P < .0001$).³⁶ While CVADs may be unavoidable, physicians should remain vigilant for signs and symptoms of VTE and remove the catheter if not required.

Our cohort's rate of hemorrhagic complications was lower than other studies. A large retrospective study presented at the American

Society of Hematology's 59th annual meeting reviewed 992 patients with PCNSL. They found an incidence of VTE of 14.4% with 16% hemorrhagic complications, mostly consisting of ICH followed by gastrointestinal bleeding.³⁷ Information regarding the type of anti-coagulation used in their patients is unavailable at this stage, and the rate of VTE in the patients who experienced bleeding complications is unclear.

We acknowledge the limitations of our study given its retrospective nature and relatively small sample size. The strengths of our study include the uniform chemotherapy treatment regimen and adequate follow-up.

In summary, PCNSL patients treated with R-MPV chemotherapy have high rates of symptomatic and early VTE with many events occurring as an outpatient. While there is room to improve current inpatient prophylaxis for these patients, to further reduce this risk, research to optimize outpatient prophylaxis is required.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

HLAY, AS, and MG designed the research and collected the data. VH, HLAY, and MG analyzed the results. HLAY and MG wrote the paper. AS, SC, JS, GG, GPG, SP, MT, and SO critically revised the manuscript. All authors approved the final version of the manuscript for publication.

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