



Prevalence, Patterns, and Predictors of Venous Thromboembolic Events in Patients Undergoing Salvage Chemotherapy and Autologous Stem Cell Transplant for Relapsed Lymphomas



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Abstract

The majority of relapsed or refractory lymphoma patients undergo salvage chemotherapy and autologous stem cell transplant (ASCT). Data on venous thromboembolic events (VTEs) in this setting are scarce. This study aims to evaluate the incidence, pattern, and risk factors for VTEs in this group of patients across the continuum of their care. The medical records of adult patients, aged ≥ 18 years, who were diagnosed and treated at our institution from 2007 to 2017 with refractory or relapsed lymphoma and received salvage therapy followed by high-dose chemotherapy and autologous stem cell transplant were retrospectively reviewed. A total of 216 patients, with a median age of 31 (range: 19–60) years, were identified. In total, 36 (16.7%) patients had VTE, mostly in the upper extremity (n=28, 77.8%); 50.0% were related to central venous catheter. Thrombosis rates were higher among patients with high lactate dehydrogenase (LDH) (29.2% vs. 5.9%, $p < 0.001$), mediastinal involvement (25.9% vs. 11.5%, $p = 0.025$) and in patients with longer hospital stay (22.1% vs. 9.5%, $p = 0.036$). In multivariate analysis, high LDH (OR: 7.66; 95% CI: 2.79–21.04, $p < 0.001$) and mediastinal involvement (OR, 3.64; 95% CI: 1.53–8.70, $p = 0.002$) were associated with significantly higher rates of VTE. In conclusion, patients with relapsed lymphoma undergoing ASCT are at higher risk for VTE, especially those with high LDH and mediastinal involvement. Thromboprophylaxis might be considered in these settings.

Keywords: ABCL, relapsed lymphomas, venous thromboembolism, autologous stem cell transplant

Background

Salvage platinum-based chemotherapy followed by high dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) is the standard treatment for transplant-eligible patients with chemo-sensitive disease [1,2].

Based on a VTE risk assessment model (RAM) proposed by Khorona et al., lymphoma is considered among the high-risk cancer sites [3]. Venous thromboembolic rates of almost 15% were previously reported [4,5]. To identify risk factors for VTE in lymphoma patients, Antic et al. developed a 7-point scoring system (ThroLy score) that separates patients into low, intermediate and high-risk categories [6]. However, the study population included heterogeneous group of patients with both low and high grade lymphomas and most of them (85%) were newly diagnosed. ThroLy score, was externally validated in 428 patients with newly diagnosed HL and diffuse large B cell lymphoma (DLBL) [7].

In addition to the disease itself, administration of platinum-based chemotherapy [8,9], the use of central venous catheters (CVC) for stem cell collection and infusion [10], and the need for hospitalization with inability to administer thromboprophylaxis due to thrombocytopenia, are potential factors that may further increase the risk for VTE in patients with refractory or relapsed lymphomas.

Objective

Data on VTE among patients with relapsed and refractory lymphoma receiving salvage chemotherapy and ASCT are scarce. Our study aims to evaluate incidence, pattern and risk factors for VTE in this group of patients across the continuum of their care; from the identification of refractory or relapsed disease, through salvage and high-dose chemotherapy until after the transplantation.

Methods

Medical records of 216 adult patients, aged ≥ 18 years, diagnosed and treated in our institution from 2007 till 2017 with refractory or relapsed lymphoma, and have received salvage therapy followed by high-dose chemotherapy and autologous stem cell transplant were retrospectively reviewed. **Table-1** shows the patients’ characteristics.

ThroLy score was calculated using the 7-piont score at time of first-line salvage chemotherapy. These points include; previous VTE/myocardial infarction or stroke [2 points], reduced mobility (ECOG 2-4), [1 point], Body mass index [BMI] $> 30\text{kg/m}^2$ [2 points], extranodal localization [1 point], mediastinal involvement [2 points], neutrophils $< 1.0 \times 10^9/\text{L}$ [1 point] and Hb $< 10\text{ grams/dL}$ [1 point]. In addition, bulky disease was defined as maximal tumor size more than 10cms.

Feature	Number (%)	Feature	Number (%)
Median age (range) yr	31 (18-60)	Extranodal involvement	
Gender		Yes	81 (37.5%)
Male	122(56.4%)	No	135 (62.5%)
Female	94 (43.6%)	High LDH	89 (41.2%)
Body Mass Index (BMI)		Bulky disease	67 (31%)
≤ 30	61 (28.2)	Mobilizing regimen	
> 30	155 (71.7%)	DHAP	145 (67.1%)
Lymphoma type		ICE	33 (15.3%)
Hodgkin's lymphoma	140 (64.8%)	Cy-GCSF	19(8.8%)
Diffuse Large B-Cell Lymphoma	54(25%)	GCSF	12 (5.5%)
Mantle cell lymphoma	10 (4.6%)	Others	7 (3.2%)
Follicular lymphoma	6 (2.8%)	Median number of salvage regimens	1 (1-7)
T-Cell lymphoma	6 (2.8%)	Disease status before transplant	
Response to first line chemotherapy		CR	81 (37.5%)
Complete response	122 (56.5%)	PR	130 (60.2)
Refractory	94 (43.5%)	SD	5 (2.3%)
Mediastinal disease on relapse		High ThroLy score > 3	46 (21%)
Present	85 (39.4%)		
Absent	131 (60.6%)		

Table-1: Patients’ Characteristics

Results

Venous Thromboembolism: VTEs were reported in 36 (16.7%) patients; majority (n=29, 80.5%) were diagnosed after salvage therapy and within 30 days of chemotherapy (34.4%). At time of VTE, most (n=26, 72.2%) of the patients had active disease and 25 (69.4%) had been admitted within 30 days.

Upper extremity VTE was the most common site for the clot (n=28, 77.8%) and 18 (50.0%) had CVC at time of VTE diagnosis. The median time for VTE was 35 days (range: 29-198) following ASCT.

All VTE were treated with low molecular weight heparin (LMWH). The median duration of anticoagulation was 6 months [range: 3-9 months]. Four (11.1%) patients had recurrence of VTE; 3 of them had refractory disease following ASCT. No significant bleeding episodes were reported.

Univariate and multivariate analysis: High LDH (29.2% vs. 5.9%, $p < 0.001$), mediastinal involvement (25.9% vs. 11.5%, $p = 0.025$) and hospital stay ≥ 25 days (22.1% vs.9.5%, $p = 0.036$) were significantly associated with increased risk of VTE .

When these factors were studied by multivariate logistic regression method, high LDH (OR: 7.66; 95% CI: 2.79-21.04, $p < 0.001$) and mediastinal involvement (OR, 3.64; 95% CI: 1.53-8.70, $p = 0.002$) were associated with significantly higher rates of VTE, **Table-2**.

Survival: After median follow up of 65.1months, 144 (66.7%) patients were still alive. People with no VTE had better median survival (166 vs 91 months), but the difference was not statistically significant ($p = 0.195$). Additionally, 5-year survival rates for both groups were 81.7% and 80.6% respectively ($p = 0.936$), **Figure -1**.

Factors	Coef	SE Coef	95% CI	Z value	P value
Mediastinal Involvement	1.215	0.439	(0.355, 2.074)	2.77	0.006
Elevated LDH	1.925	0.507	(0.932, 2.918)	3.80	0.000
> 25 days hospital stay	0.858	0.438	(0.001, 1.717)	1.96	0.050

Table-2: Multivariate analysis.

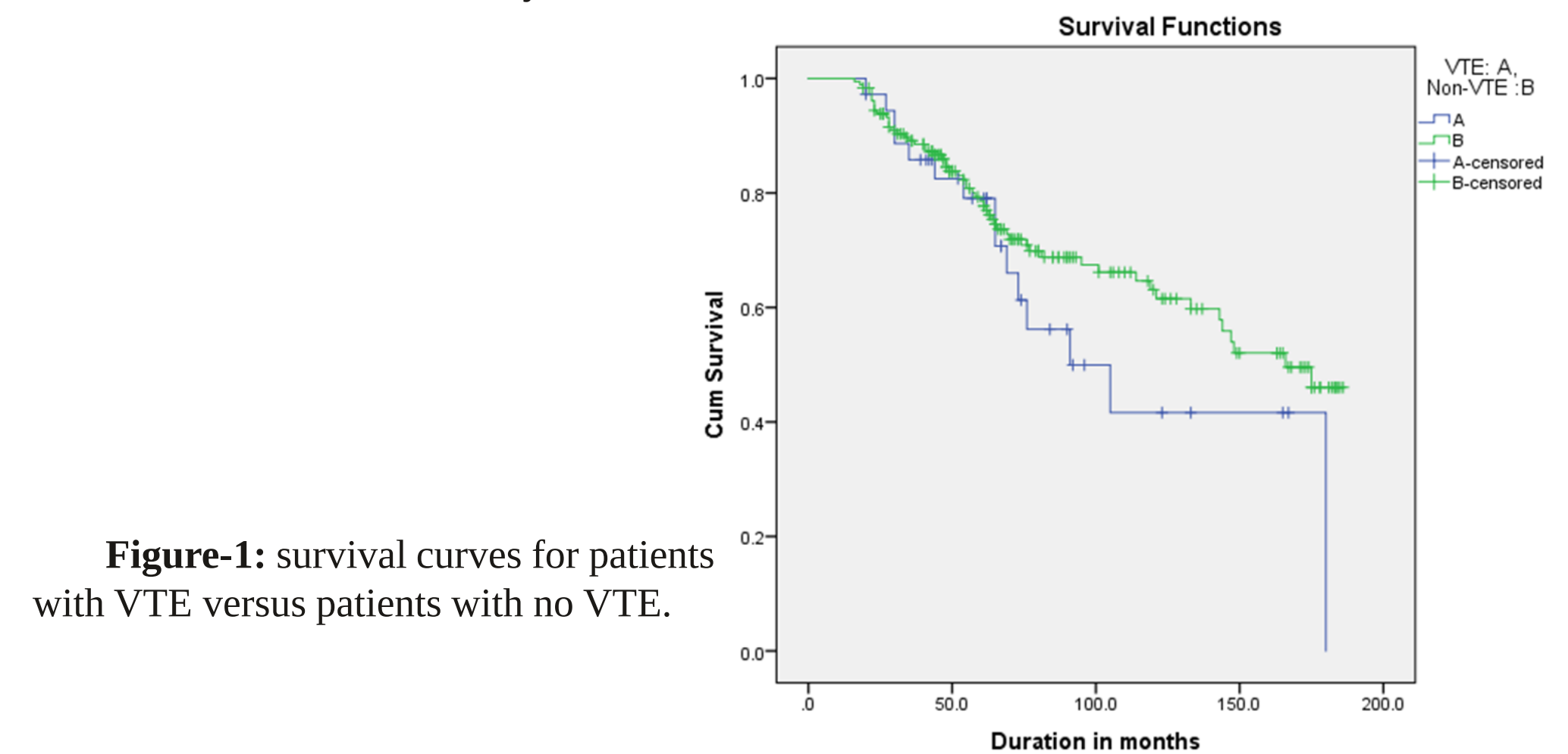


Figure-1: survival curves for patients with VTE versus patients with no VTE.

Discussion

The overall incidence of VTE in our study (16.9%) is a little lower than what has been recently reported in a similar group of patients (23%) [11].

Risk factors for VTE in lymphoma patients undergoing ASCT were variably identified. For example, in the study by Conlan et al., VTE were more common in Hodgkin lymphoma patients [12], while previous history of VTE was the only factor that was significantly associated with VTE in the study by Hegerova et al.[13].In our study, we confirmed the previous assumption that mediastinal involvement, rather than lymphoma subtype, increased the risk for VTE .

In our data, patients with high ThroLy score had higher incidence of VT when compared to patient with low scores(21.3% vs 13.1%), but this difference wasn't statistically significant on univariate analysis. Interestingly, mediastinal involvement at time of relapse was more significant than the ThroLy score.

Most of VTE reported in previous studies were catheter- related . However, only half of VTE reported in our study were CVC related, and disease related variables contributed more significantly to the development of VTE. Hospitalization is well known to increase the risk VTE [14]. Our data showed that patients who needed prolonged hospitalization (≥ 25 days) at the time of HDC and ASCT, had higher incidence of VTE.

Our study also showed that VTE had no negative impact on patients' survival. This is consistent with what was recently reported [14]. Possibly, other factors including relapse and age might have a more pronounced effect on the survival of such patients.

Conclusion

In conclusion, VTE are common in relapsed lymphoma patients receiving platinum-based salvage chemotherapy, HDC and ASCT. Prompt evaluation for VTE related symptoms is advised. Patients with high LDH and mediastinal involvement at time of relapse, might be considered for prophylactic anticoagulation if no contraindications exist.

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