Review article

Haematol J Bangladesh 2023;7(1):52-58
https://journal.hematologybd.org/index.php/haematoljbd
ISSN: 2523-1219 (print)
ISSN: 2707-1405 (online)

Overview of Venous Thromboembolism (VTE) in Patients with Haematological malignancy.

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Citation: Islam MM, Islam GY. Overview of Venous Thromboembolism (VTE) in patients with haematological malignancy. Haematol J Bangladesh. 2023;7(1):52-58.

DOI: https://doi.org/10.37545/haematoljbd2023109

Received: 09 February 2023

Accepted: 13 February 2023

Published: 20 March 2023

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ABSTRACT

Venous thromboembolism (VTE) is not uncommon in patients with haematological malignancy. ALL patients are at increased risk due to the use of L-asparaginase in different protocols. Serum fibrinogen level should be monitored and maintained above 100 mg/dL. VTE development in AML patients can be monitored by DIC scoring. Though APL is commonly associated with bleeding, thrombosis is not unseen. High WBC count (>10 × 10^9/L), Low Fibrinogen (<170 mg/dL), M3-variant subtype, use of ATRA & antifibrinolytics increases chance of thrombosis in APL. Poor prognostic factors of CLL also increase risk of VTE in those patients. Use of new-generation tyrosine kinase inhibitors (dasatinib, nilotinib, ponatinib) in CML is associated with a statistically significant increased risk of vascular occlusive event. Prophylaxis with low-dose aspirin (100 mg/day) is recommended for all polycythaemia vera patients. Low-dose aspirin prophylaxis in essential thrombocythemia is recommended only for those who have microvascular symptoms. VTE in lymphoma patient can be predicted by Khorana Score. Primary mediastinal B cell lymphoma, DLBCL, Peripheral T cell Lymphoma, Hodgkin lymphoma are more commonly related to VTE incidence. Immunomodulatory agents like thalidomide and lenalidomide increase risk of VTE in MM patients & prophylaxis with low dose aspirin or LMWH is recommended. LMWH or DOAC (apixaban, rivaroxaban) is used for treatment of VTE in haematological malignancy.

Key Words: *Venous thromboembolism (VTE), haematological malignancy, thrombosis, LMWH (Low molecular weight heparin), DOAC (Direct oral anticoagulant).*

Introduction:

Venous thromboembolism (VTE) is common in patients with cancer. Much work has been done to evaluate clinical and laboratory risk factors in solid tumours but not so much with haematological malignancy. The Khorana score focused mainly on patients with solid tumours. It is important that we parse through the available data to determine the risk of VTE in patients with haematological malignancy as the currently available risk models do not completely address this patient population.

It was previously thought that VTE is less common in haematological malignancy than solid cancer and physicians have been more concerned for bleeding

rather than thrombotic complications in such patients. But recent studies suggest that incidence of VTE may be similar, or even higher in patients with haematological malignancy than that of patients with solid cancers.[1] Concern about VTE in haematological malignancies has been emphasized by the widespread use of central venous catheters (CVC) and the introduction of new immunomodulatory agents. This review will highlight the incidence, pathogenesis and brief practical guidance for preventing and managing VTE in haematologic malignancies. Thrombotic complications following haematopoietic stem cell transplantation are not included in this review.

VTE in Acute Lymphoblastic Leukaemia (ALL):

Incidence of VTE in ALL patients is about 10.6%.[2] One of the main risk factors for the development of VTE has been the use of L-asparaginase. Other risk factors include older age (>30years), central venous (CV) line, high risk ALL, T-ALL, male gender, non-O blood group.[3] The mechanism of thrombosis by L-asparaginase is complex. L-asparaginase disrupts the physiologic balance between the haemostatic and anticoagulation pathways, along with activation of platelets and endothelial cells. L-Asparagenase decreases level of proteins C, S and antithrombin III and this contributes to an increased risk of thrombosis.[4,5]

Patients especially high-risk patients should be monitored for VTE. Use of L-asparaginase therapy is associated with reduced levels of antithrombin and fibrinogen; hence studies have investigated the role of fresh frozen plasma (FFP) or cryoprecipitate supplementation to reduce the thrombohaemorrhagic risk of L-asparaginase therapy. Fibrinogen <50 mg/dL increased the likelihood of thrombosis. There are different consensus whether 50 or 100 mg/dL should be the cut-off value. To maintain S. fibrinogen 100 mg/dL appears to be safer.[6] FFP or cryoprecipitate can be transfused to restore fibrinogen level. FFP or cryoprecipitate can be given empirically after each dose of L-asparagenase in patient with low S. fibrinogen if monitoring is not done.

ALL patient with VTE should be treated with low molecular weight heparin (LMWH), CV line should be removed (if the patient have any), L-Asparagenase should be stopped. L-Asparagenase can be restarted 4-8 weeks after starting anticoagulant. Rest of the dose should be given under anticoagulant coverage. Anticoagulant can be stopped after end of all doses of L-Asparagenase. In adults and in high-risk patients anticoagulant should be used until the end of chemotherapy.[5]

VTE in Acute Myeloid Leukaemia (AML):

Incidence of VTE in AML patients is 4.2% (within 6 month of diagnosis).[7] VTE risk factors are less clear in AML patients. A recent study suggested that disseminated intravascular coagulation (DIC) scoring could effectively predict thrombotic events in AML patients.[8] According to this study a high DIC score (a score of 5 or more) is associated with venous and arterial thrombosis with a hazard ratio of 4.8 (DIC was scored as per the International Society on Thrombosis and Haemostasis guidelines, Table I).[9]

Table I: DIC Score according to ISTH (International Society on Thrombosis and Haemostasis)

Parameter	Result	Score
Platelet count	>100×10^9/l	0
	<100×10^9/l	1
	< 50×10^9/l	2
Prothrombin Time	<3s prolonged	0
	>3s but <6s	1
	>6s	2
Fibrinogen	>1.0g/l	0
	<1.0g/l	1
FDP/D-Dimer	No increase	0
	Moderate increase	2(250-5,000)
	Strong increase	3(>5,000)

A total score of ≥5 = DIC as long as the score is associated with a clinical disorder known to cause DIC.

VTE in Acute Promyelocytic Leukaemia (APL):

APL is commonly associated with DIC. Haemorrhagic complications of APL is well known but thrombosis is not uncommon. Six month cumulative incidence of VTE is 8.4% in the APL patients.[2] It has been postulated that the imbalance caused by all-trans retinoic acid (ATRA) between procoagulant and fibrinolytic forces induce a prothrombotic affect.[10] The combined use of ATRA and antifibrinolytic agents has been hypothesized as further increasing the risk for thrombosis in some case reports.[11] But it may be difficult to determine, whether thrombosis in APL is attributable to hypercoagulability caused by the disease itself versus a drug affect from ATRA. High WBC count (>10 × 10^9/L), Low Fibrinogen (<170 mg/dL), M3-variant subtype (micro-granular), haemoglobin >10 g/dL are considered risk factor for thrombosis in APL. Low fibrinogen levels has statistical significance for predicting thrombosis.[12] Low molecular weight heparin or fondaparinux can be used in coagulopathy associated with APL. Antiadhesive qualities of low molecular weight heparin, which have been noted to decrease the interaction of cancer cells with the endothelium in vitro, may prevent the development of the retinoic acid syndrome in patients with APL with high leukocyte counts.[13]

VTE in chronic lymphocytic leukaemia (CLL):

Incidence of VTE in CLL patients is not well studied. CLL has a VTE rate of 1.45% per patient year of follow-up.[14] Poor prognostic factors for CLL, concurrent other malignancy, age, performance status, are all associated with VTE occurrence.[14]

VTE in Chronic Myeloid leukaemia (CML):

Venous and arterial vascular events in CML is mainly related to use of tyrosine kinase inhibitors (TKI). Use of new-generation tyrosine (dasatinib, nilotinib, ponatinib) kinase inhibitors is associated with a statistically significant increased risk of vascular occlusive events than Imatinib.[15]

VTE in Myeloproliferative Neoplasms (MPN):

VTE, common in MPN, includes polycythaemia vera, essential thrombocythaemia and primary myelofibrosis. It has been estimated that thrombosis is present in 12%-39% of patients with polycythaemia vera, 10%-29% with essential thrombocythaemia and around 13% of myelofibrosis at the time of diagnosis.[16,17] Prophylaxis with low-dose aspirin (100 mg/day) is recommended for all polycythaemia vera patients.[18] Low-dose aspirin prophylaxis in essential thrombocythaemia is less established, due to the fact that patients with a platelet count >1500 × 10^9/L are at increased bleeding, rather than thrombotic risk[19], due to pseudo-von Willebrand disease. But essential thrombocythaemia patients with microvascular symptoms, including erythromelalgia and transient neurological and ocular disturbances are recommended to take low-dose aspirin.[20] For treatment of VTE LMWH should be used for Six months.[21]

VTE in lymphoma:

VTE in lymphoma patient can be predicted by Khorana Score.[22] But heterogeneity of lymphoma sub-types including differences in tissue histology, tumour burden and sites of involvement complicates the use Khorana score in lymphoma patient (Table II). New predicting models are developing to address lymphoma alone. Incidence of VTE is more in aggressive lymphomas than in low-grade lymphoma (4.2% vs 1.8%).[23] Primary mediastinal B cell lymphoma, DLBCL, Peripheral T cell Lymphoma, Hodgkin lymphoma are more commonly related to VTE incidence.[23,24]

Table II: Khorana Score

Patient Characteristics	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecologic, genitourinary excluding prostate)	1
Platelet counts ≥350,000 per mm^3	1
Leukocyte counts >11,000 per mm^3	1
Haemoglobin <10 g/dL or use of ESAs	1
BMI ≥35 kg/m^2	1

BMI - body mass index; ESA - erythropoiesis- stimulating agent. High-risk = score ≥3; Intermediate risk = Score ≥1; Low-risk = Score 0

For low-risk ambulatory patient no thromboprophylaxis is recommended, for intermediate risk patient no thromboprophylaxis or prophylaxis with Direct Oral Anticoagulant (DOAC - apixaban or rivaroxaban) is recommended, for high-risk ambulatory patient prophylaxis with LMWH or DOAC is recommended.[25] For patient with lymphoma and active VTE DOAC (apixaban, rivaroxaban) or LMWH can be used for initial treatment.[25]

VTE in Multiple Myeloma:

VTE in Multiple Myeloma patients has got more attention after introducing immunomodulatory agents like thalidomide and lenalidomide. Use of bortezomib (even with erythropoiesis-stimulating agent) is not associated with risk of VTE.[26] Prophylaxis for VTE is recommended for patients receiving thalidomide or lenalidomide. Low dose aspirin is recommended in low-risk patients receiving thalidomide or lenalidomide, i.e., those with one or no risk factor. Prophylactic doses of LMWH (or full intensity warfarin anticoagulation with an INR between 2 and 3) are recommended for high-risk patients receiving thalidomide or lenalidomide, i.e., those with more than one risk factors. Patients receiving thalidomide or lenalidomide are considered high risk when concomitant high dose dexamethasone, doxorubicin or multiagent chemotherapy are used or when more than one risk factor for VTE is present (i.e., age, obesity, CV line, co-morbidities such as diabetes, infections or cardiovascular diseases, immobility, history of VTE, inherited thrombophilia and myeloma related hyperviscosity).[27]

Treatment of VTE and Platelet count:

LMWH is usually preferred for treatment. Direct oral anticoagulants apixaban and rivaroxaban are acceptable alternative.[28] Platelet count always make it difficult to treat VTE in patient with haematological malignancy. It is safe to administer full dose enoxaparin for a platelet count > 50×10^9 per litre. We can administer half-dose enoxaparin for a platelet count of 25 - 50×10^9 per litre and hold anticoagulation for a platelet count < 25×10^9 per litre.[29]

Conclusion:

VTE is not uncommon in haematological malignancy. But most of the diseases do not have any clear-cut guideline for monitoring, prophylaxis and treatment. Prospective comparison of VTE prophylaxis versus no prophylaxis in patient undergoing L-Asparaginase (in ALL) and immunomodulatory drugs (MM) should be carried out. Separate risk scoring system should be established for lymphoma. Guidelines based on clinical trials should be established for management of VTE with thrombocytopenia.

Table III: Summary of VTE management in haematological malignancy

Type of malignancy	Special Consideration in risk of VTE	Monitoring/ Scoring	Prophylaxis	Treatment
ALL	L Asparagenase treatment can increase risk	S. Fibrinogen, Antithrombin III	FFP/cryoprecipitate may be used	LMWH/DOAC
AML		DIC Score	No prophylaxis recommendation	
APL	ATRA and antifibrinolytic use, High Count, M3- varient	DIC Score, S. Fibrinogen, Platelet count		
CLL	Poor CLL prognostic Increased risk	No recognized tool or Lab test		
CML	2nd and 3rd Gen TKI increased risk Thrombosis	No recognized tool or Lab test		
PRV	Arterial thrombosis is common		Low Dose Aspirin	
ET	Platelet >1500x10^9 risk of bleeding		Low Dose Aspirin in Pt with microvascular symptoms	
Lymphoma	High grade Lymphoma has more risk, stage, site, use of doxorubicin	Use Khorana score to start prophylaxis	DOAC or LMWH for high-risk patient	
MM	Thalidomide and Lenalidomide use	Risk assessment by drugs, age, obesity, DM & others. (see text for detail)	Low-risk - Low dose aspirin High-risk - LMWH	

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