Received: 11 April 2018 | Accepted: 19 April 2018

DOI: 10.1002/rth2.12111

BRIEF REPORT

rpth research & practice in thrombosis & haemostasis

Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: A systematic review

Bethany R. Samuelson Bannow MD[1] | Agnes Y. Y. Lee MD[2] | Alok A. Khorana MD[3] | Jeffrey I. Zwicker MD[4] | Simon Noble MD[5] | Cihan Ay MD[6] | Marc Carrier MD[7]

[1]Division of Hematology, Department of Medicine, Oregon Health & Science University, Portland, OR, USA

[2]Division of Hematology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada

[3]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

[4]Division of Hemostasis and Thrombosis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

[5]Cottingham Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff, Wales, UK

[6]Clinical Division of Hematology and Hemostaseology, Department of Medicine, Medical University of Vienna, Vienna, Austria

[7]Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, ON, Canada

Correspondence
Marc Carrier, Ottawa Hospital, Ottawa, ON, Canada.
Email: mcarrier@toh.ca

Abstract

Background: The management of anticoagulation for cancer-associated thrombosis (CAT) in patients with thrombocytopenia is controversial. Whereas some studies suggest that administration of reduced-dose low-molecular-weight heparin (LMWH) or temporary discontinuation for moderate and severe thrombocytopenia may be a safe and effective, others suggest full-dose anticoagulation with transfusion support. We sought to address this important knowledge gap and summarize the literature comparing these two common management strategies.

Methods: A systematic review of the literature (PROSPERO CRD42017077127) using MEDLINE (inception to September 2017) was conducted. We included studies that reported recurrent venous thromboembolism (VTE) and major bleeding complications among patients treated with both of the two most common management strategies: therapeutic anticoagulation with platelet transfusion support and dose-modified anticoagulation for periods when the platelet count is $<50 \times 10^9$/L.

Results: A total of 134 article records were identified on the initial search and 10 articles underwent full text review. Two observational studies met the inclusions criteria. A total of 121 patients with CAT and thrombocytopenia were included. Forty-two of these patients had pulmonary embolism and 87 had deep vein thrombosis (DVT) including 38 upper extremity DVT. Overall, 27% of patients, regardless of their treatment strategy, experienced recurrent VTE. Thirteen percent of anticoagulated patients (15% of all patients) experienced a major bleeding episode. Meta-analysis could not be conducted.

Conclusions: Our findings do not support one management strategy over another to treat CAT patients with thrombocytopenia. However, the data highlights the heightened risk of recurrent VTE in this patient population despite the thrombocytopenia.

KEYWORDS

hemorrhage, neoplams, thrombocytopenia, venous thromboembolism, venous thrombosis

Essentials

- The management of anticoagulation in patients with thrombocytopenia is controversial.
- Some studies suggest to administer reduced-dose low-molecular-weight heparin (LMWH).
- While other studies suggest full-dose anticoagulation using LMWH and transfusion support.
- The results from our systematic review do not support one management strategy over another.

1 | INTRODUCTION

Venous thromboembolism (VTE) affects between 1% and 8% of all patients undergoing cancer therapy and is the second leading cause of death among outpatients undergoing chemotherapy.[1,2] Management of cancer-associated thrombosis (CAT) requires special considerations and is different from the management of VTE in non-cancer patients.[3] It is made more challenging by the presence of other complications of cancer therapy, such as thrombocytopenia, which is common among patients undergoing chemotherapy for hematologic malignancy and certain solid tumors. While thrombocytopenia has not shown any protective benefits against recurrent VTE among CAT patients, it has been associated with increased rates of bleeding.[4] Therefore, the management of anticoagulation in this patient population requires special attention.

Low-molecular-weight heparin (LMWH) is known to reduce the risk of VTE recurrence and is currently recommended by all clinical practice guidelines for the initial treatment of CAT.[5] However, its optimal dosing for the management of CAT in patients with thrombocytopenia is unknown. Whereas some studies suggest that administration of reduced-dose LMWH for moderate thrombocytopenia (platelet counts $<50 \times 10^9$/L) and temporary discontinuation for severe thrombocytopenia (platelet counts $<25 \times 10^9$/L) may be a safe and effective, others suggest full-dose anticoagulation with transfusion support in thrombocytopenia.[6,7] We sought to address this important knowledge gap and summarize the literature comparing these two common management strategies for the management of anticoagulation in the setting of CAT and thrombocytopenia: full dose anticoagulation with platelet support and dose-modified LMWH.

2 | METHODS

This systematic review was registered on PROSPERO (registration number CRD42017077127). We searched Medline (inception to September 2017) for relevant articles. Search terms included ("neoplasms"[MeSH Terms] AND "thrombocytopenia"[MeSH Terms]) AND "anticoagulants"[MeSH Terms]). Articles were included if they reported outcomes for patients treated for CAT during periods of treatment-related thrombocytopenia. Articles were excluded if they did not report recurrent VTE and bleeding outcomes separately for patients treated with both a dose-modified strategy and a full-dose strategy with transfusion support or were case reports/series including ≤5 patients.

The primary efficacy and safety measures was recurrent VTE and major bleeding episodes, respectively. Recurrent VTE was defined as symptomatic, imaging-confirmed progression of index thrombosis or thrombosis at a new site. Major bleeding episode was defined as per the International Society of Thrombosis and Haemostasis definition.[8]

Quality assessments of the observational studies were carried out using the ROBINS-1 tool from the Cochrane Method group (Supplementary Appendix S1).[9]

3 | RESULTS AND DISCUSSION

A total of 134 article records were identified on the initial search and 10 articles underwent full text review. Of these, six were excluded for failing to include patients undergoing management according to both treatment strategies,[6,10-14] one was excluded for failure to report outcomes of both strategies[7] and one was excluded for study design (case series of only five patients).[15] The remaining two studies were included and are described below. Ten studies which were excluded due to only utilizing one treatment strategy are outlined in Table 1 for comparison.[12,15–20]

Overall, 121 patients with CAT and thrombocytopenia were included in our review (Table 2). Forty-two of these patients had pulmonary embolism (PE) and 87 had deep vein thrombosis (DVT) including 38 upper extremity DVT (several patients had multiple events at different locations).

The first study was a retrospective cohort study of 74 patients with CAT and thrombocytopenia defined as a platelet count $<100 \times 10^9$/L.[23] Patients were categorized according to three different management groups: no antithrombotic therapy, complete course of antithrombotic therapy consisting of therapeutic dose anticoagulation given daily for ≥3 months, or partial antithrombotic therapy indicating a course of anticoagulation with reduced dose intensity, duration, or continuity. Patients receiving full-dose anticoagulation had a higher median platelet count at the time of the VTE event and at nadir, had a shorter duration of thrombocytopenia, were more likely to have a PE or lower extremity DVT (and less likely to have upper extremity DVT) and were less likely to receive platelet transfusions. Seventeen subjects received no anticoagulation, 27 received partial antithrombotic therapy, and 30 patients received a complete course of antithrombotic therapy. A total of 23 recurrent VTE events and 13 major bleeding episodes were reported (Table 2). The majority of recurrent VTE events occurred in patients receiving

TABLE 1 Outcomes of anticoagulation strategies in thrombocytopenic hematologic malignancy patients

Author (year)	Design	Treatment strategies (n)	Recurrence	Bleeding events	Duration of follow-up
Khanal (2016)[21a]	Retrospective cohort	Therapeutic LMWH or VKA (15)	5	4	24.6 months
		Prophylactic/reduced LMWH (22)	3	1	
Campbell (2017)[7]	Case series	Therapeutic LMWH or UFH (13)	1	1	6 months
Li (2017)[18]	Retrospective cohort	LMWH/UFH (132)	2	20	359 days
		No anticoagulation (72)	1	10	
Houghton (2017)[17]	Retrospective cohort	Anticoagulation (45)	1	12	100 days
		No anticoagulation (33)	5	1	
Drakos (1992)[16]	Case series	Prophylactic/reduced LMWH (5)	0	0	NR
Lim (2016)[15]	Case series	Therapeutic LMWH (1)	0	0	NR
		Prophylactic/reduced LMWH (3)	0	2	
		No anticoagulation (1)	0	0	
Oliver (2015)[22]	Retrospective cohort	Therapeutic LMWH (13)	0	5	6 months
		Prophylactic/reduced LMWH (8)	0		
		No anticoagulation (14)	0	1	
Imberti (2004)[12]	Case series	Therapeutic LMWH[b]	0	0	NR
Ibrahim (2005)[9]	Case series	Prophylactic/reduced LMWH (26)	NR	6	NR
Schimmer (1998)[20]	Retrospective cohort	Therapeutic UFH (10)	NR	3	NR
Kopolovic (2015)[23]	Retrospective cohort	Full anticoagulation (30)	8	2	3 months
		Partial anticoagulation (27)	12	9	
		No anticoagulation (17)	3	2	
Samuelson (2017)[24]	Retrospective cohort	Therapeutic LMWH or UFH (82)	5	33	30 days

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin-K antagonist.
[a]Study included patients with platelets >50, only those with platelets <50 included here.
[b]LMWH was dose reduced for platelets <20.

no anticoagulation, followed by patients receiving prophylactic or intermediate doses of anticoagulation (partial anticoagulation). The majority of major bleeding episodes were reported in patients receiving partial anticoagulation, followed by patients receiving no anticoagulation. Univariate logistic regression models reported an increased risk of recurrent VTE for patients with hematologic malignancy (OR 11.0; 95% CI: 1.36-88.66), thrombocytopenia lasting longer than 1 month (OR 4.67; 95% CI: 1.23-17.74) and patients with an index upper extremity DVT (OR 4.10; 95% CI: 1.45-11.63). The risk of recurrent VTE seemed lower among patients receiving full therapeutic doses of LMWH (OR 0.13; 95% CI: 0.03-0.58) as well as for those with index PE (OR 0.17; 95% CI: 0.04-0.64). The risk of major bleeding episodes seem higher among patients with a prior history of hemorrhage (OR 6.33; 95% CI: 1.34-29.96) in this patient population.

The second identified study was a retrospective cohort study including 47 patients with CAT and thrombocytopenia (platelets <50 x10^9/L) and 81 patients without thrombocytopenia.[25] Among the thrombocytopenic patients, 14 received therapeutic anticoagulation with LMWH and 22 received dose-modified LMWH (enoxaparin 40 mg daily during the period of significant thrombocytopenia). Median follow-up was 24.6 months in thrombocytopenic patients. Differences between subjects receiving different treatments within the thrombocytopenic group were not reported. Eleven and 5 patients had a recurrent VTE and major bleeding episode, respectively (Table 2). Four of the five major bleeding events occurred in patients receiving therapeutic anticoagulation. Two of the 11 recurrent VTE events occurred in patients receiving therapeutic anticoagulation.

A quality assessment of each study was performed using the ROBINS-1 method.[25] Both studies were judged to be at serious risk of bias in two domains (confounding and selection of reported results) but not at critical risk of bias in any domain.

TABLE 2 Recurrent VTE and Hemorrhage rates in included studies

Anticoagulation strategy	Recurrent VTE				Bleeding (Major & CRNMB)			
	Therapeutic n = 44	Dose-modified n = 49	None n = 26	Total n = 119	Therapeutic n = 44	Dose-modified n = 49	None n = 26	Total n = 119
Kopolovic et al. n = 74	3/30 (10%)	12/27 (44%)	8/17 (47%)	23/74 (31%)	2/30 (7%)	9/27 (33%)	2/17 (12%)	13/74 (18%)
Khanal et al. n = 47[a]	4/14 (29%)	3/22 (14%)	2/9 (22%)	9/45 (20%)[a]	4/14 (29%)	1/22 (4.5%)	0	5/45 (11%)
Total	7/44 (16%)	15/49 (31%)	10/26 (38%)	32/119 (27%)	6/44 (14%)	10/49 (20%)	2/26 (8%)	18/119 (15%)

CRNMB, clinically relevant non-major bleeding; VTE, venous thromboembolism.
[a]One patient received anticoagulation with warfarin, one had no outcomes.

The optimal management of CAT with anticoagulation in thrombocytopenic patients is an important and frequent challenge facing clinicians. Our systematic review was only able to identify two observational studies reporting recurrent VTE and major bleeding complications among patients treated with both of the two most common management strategies: therapeutic anticoagulation with platelet transfusion support and dose-modified anticoagulation for periods when the platelet count is $<50 \times 10^9$/L.

Both studies reported high risk of recurrent VTE despite thrombocytopenia. Overall, 27% of patients, regardless of their treatment strategy, experienced recurrent VTE. This is striking even in the context of the known higher rates of recurrent VTE commonly seen in patients with CAT. For example, in the CLOT trial, a rate of recurrence of 17% in the oral anticoagulant arm was considered to be unacceptably high in comparison to a rate of 9% among patients treated LMWH.[3] This adds to a growing body of literature supporting the fact that thrombocytopenia, while accompanied by an increased rate of bleeding in cancer patients, is not accompanied by a decreased rate of VTE complications.[24,26,27]

The rate of major bleeding episodes, on the other hand, was more modest and nearly half the reported rate of recurrent VTE. Thirteen percent of anticoagulated patients (15% of all patients) experienced a major bleeding episode. This rate is consistent with a previously published study among patients with treatment-related thrombocytopenia not receiving anticoagulation.[4]

The best anticoagulation strategy (full-dose anticoagulation with platelet support or dose-modified LMWH) to use in patients with CAT and thrombocytopenia remains unclear. The results of the study by Kopolovic and colleagues support the concept that continuous, therapeutic anticoagulation offers a lower risk of recurrent VTE with a similar rate of bleeding complication, whereas the by Khanal and colleagues suggest that a dose-modified strategy might result in both lower rates of VTE and major bleeding complications. The findings were similarly mixed in studies excluded from this review for investigating only one of the two strategies. Both VTE recurrence and bleeding rates were high, particularly in the acute period, and were seen across treatment strategies, including holding of anticoagulation. No study identified a distinct platelet threshold below which a modified strategy (either transfusion support or dose reduction) improved outcomes.

Both included studies had numerous limitations that are important to highlight. The studies were retrospective, nonrandomized, and subject to high rates of bias. It is also unclear if the target platelet threshold was maintained in patients with thrombocytopenia receiving full-dose anticoagulation. Decisions regarding which strategy to use were likely dependent on multiple factors, including patient characteristics not addressed in this study and provider experience and judgment. Patients whose clinical characteristics suggested they were at high risk of recurrent VTE were likely preferentially given full dose anticoagulation and patients thought to be at either low risk of recurrence or high risk of bleeding likely received reduced dose or no anticoagulation. Ultimately prospective, randomized trials are

desperately needed to adequately compare these two anticoagulation management strategies and provide guidance to clinicians.

Our review has a number of limitations, the most important one is the small number of included studies and lack of any randomized, controlled trials. Additionally there was a large degree of heterogeneity between studies, including population (thrombocytopenia defined differently), intervention (dosing) length of follow-up and definition of outcomes. This, in addition to the small sample size, prohibited pooling of data.

In conclusion, our findings do not support one management strategy over another to treat CAT patients with thrombocytopenia. However, the data highlights the heightened risk of recurrent VTE in this patient population despite the thrombocytopenia. Therefore, clinicians should consider initiating anticoagulation (therapeutic or reduced-dose LMWH) in the absence of absolute contraindications for these patients.

RELATIONSHIP DISCLOSURE

Dr. Samuelson Bannow reports grants from NHLBI during the conduct of the study. Dr. Lee reports personal fees from Bayer, personal fees from Pfizer, grants from BMS, personal fees from LEO Pharma, outside the submitted work. Dr. Khorana reports grants from Janssen, grants from Bayer, grants from Pfizer, grants from Sanofi, outside the submitted work. Dr. Zwicker reports grants from Quercegen and Incyte, personal fees from Parexel and Daiichi, during the conduct of the study. Dr. Noble has nothing to disclose. Dr. Ay has nothing to disclose. Dr. Carrier reports grants and personal fees from Leo Pharma, grants and personal fees from BMS-Pfizer, personal fees from Bayer, Pfizer, Sanofi, Servier, outside the submitted work.

AUTHOR CONTRIBUTION

BS and MC developed the study concept and design, performed the systematic review, data extraction, data analysis, and authored the manuscript. AL, AK, JZ, CA, and SM authored the manuscript, helped with data analysis, and provided critical revisions to the manuscript.

ORCID

C Ay http://orcid.org/0000-0003-2607-9717

REFERENCES

1. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5:632–4.
2. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122:1712–23.
3. Lee AY, Levine MN, Baker RI, et al. CLOT Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146–53.
4. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. 2010;362:600–13.
5. Streiff MB. The National Comprehensive Cancer Center Network (NCCN) guidelines on the management of venous thromboembolism in cancer patients. Thromb Res. 2010;125:S128–33.
6. Mantha S, Miao Y, Wills J, Parameswaran R, Soff GA. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. J Thromb Thrombolysis. 2017;43:514–8.
7. Campbell PM, Ippoliti C, Parmar S. Safety of anticoagulation in thrombocytopenic patients with hematologic malignancies: a case series. J Oncol Pharm Pract. 2017;23:220–5.
8. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13:2119–26.
9. Ibrahim RB, Peres E, Dansey R, et al. Safety of low-dose low-molecular-weight-heparins in thrombocytopenic stem cell transplantation patients: a case series and review of the literature. Bone Marrow Transplant. 2005;35:1071–7.
10. Herishanu Y, Misgav M, Kirgner I, Ben-Tal O, Eldor A, Naparstek E. Enoxaparin can be used safely in patients with severe thrombocytopenia due to intensive chemotherapy regimens. Leuk Lymphoma. 2004;45:1407–11.
11. Ibrahim RB, Stroempl LE, Abella EM, Racine E. Enoxaparin safety in patients with severe thrombocytopenia. Ann Pharmacother. 2002;36:1478–9.
12. Imberti D, Vallisa D, Anselmi E, et al. Safety and efficacy of enoxaparin treatment in venous thromboembolic disease during acute leukemia. Tumori. 2004;90:390–3.
13. Monreal M, Zacharski L, Jimenez JA, Roncales J, Vilaseca B. Fixed-dose low-molecular-weight heparin for secondary prevention of venous thromboembolism in patients with disseminated cancer: a prospective cohort study. J Thromb Haemost. 2004;2:1311–5.
14. Saccullo G, Malato A, Raso S, et al. Cancer patients requiring interruption of long-term warfarin because of surgery or chemotherapy induced thrombocytopenia: the use of fixed sub-therapeutic doses of low-molecular weight heparin. Am J Hematol. 2012;87:388–91.
15. Lim MS, Enjeti AK. Safety of anticoagulation in the treatment of venous thromboembolism in patients with haematological malignancies and thrombocytopenia: report of 5 cases and literature review. Crit Rev Oncol Hematol. 2016;105:92–9.
16. Drakos PE, Nagler A, Or R, Gillis S, Slavin S, Eldor A. Low molecular weight heparin for Hickman catheter–induced thrombosis in thrombocytopenic patients undergoing bone marrow transplantation. Cancer. 1992;70:1895–8.
17. Houghton DE, Key NS, Zakai NA, Laux JP, Shea TC, Moll S. Analysis of anticoagulation strategies for venous thromboembolism during severe thrombocytopenia in patients with hematologic malignancies: a retrospective cohort. Leuk Lymphoma. 2017;58:2573–81.
18. Li A, Davis C, Wu Q, Kesten MF, Gopal AK, Garcia DA. Management of anticoagulation in patients with hematologic malignancy undergoing autologous hematopoietic cell transplantation. Blood. 2017;1:707–14.
19. Samuelson BT, Gernsheimer T, Estey E, Garcia DA. Variability in management of hematologic malignancy patients with venous thromboembolism and chemotherapy-induced thrombocytopenia. Thromb Res. 2016;141:104–5.
20. Schimmer AD, Stewart AK, Keating A, et al. Safety of therapeutic anticoagulation in patients with multiple myeloma receiving

autologous stem cell transplantation. Bone Marrow Transplant. 1998;22:491–4.
21. Khanal N, Bociek RG, Chen B, et al. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. Am J Hematol. 2016;91:E468–72.
22. Oliver N, Short B, Thein M, et al. Treatment of catheter-related deep vein thrombosis in patients with acute leukemia with anticoagulation. Leuk Lymphoma. 2015;56:2082–6.
23. Kopolovic I, Lee AY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. Ann Hematol. 2015;94:329–36.
24. Samuelson Bannow BT, Walter RB, Gernsheimer TB, Garcia DA. Patients treated for acute VTE during periods of treatment-related thrombocytopenia have high rates of recurrent thrombosis and transfusion-related adverse outcomes. J Thromb Thrombolysis. 2017;44:442–7.
25. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
26. Cortelezzi A, Moia M, Falanga A, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study. Br J Haematol. 2005;129:811–7.
27. Refaei M, Fernandes B, Brandwein J, Goodyear MD, Pokhrel A, Wu C. Incidence of catheter-related thrombosis in acute leukemia patients: a comparative, retrospective study of the safety of peripherally inserted vs. centrally inserted central venous catheters. Ann Hematol. 2016;95:2057–64.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Samuelson Bannow BR, Lee AYY, Khorana AA, et al. Management of anticoagulation for cancer-associated thrombosis in patients with thrombocytopenia: A systematic review. *Res Pract Thromb Haemost*. 2018;2:664–669. https://doi.org/10.1002/rth2.12111