Anti-Xa monitoring of low-molecular-weight heparin in adult patients with cancer

Lisa Baumann Kreuziger[1] *and Michael Streiff*[2]

[1]*BloodCenter of Wisconsin, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI, and* [2]*Department of Medicine, Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD*

A 68-year-old man developed a right femoral vein deep vein thrombosis and bilateral pulmonary embolism while receiving chemotherapy for stage IV prostate cancer. His creatinine at diagnosis is 1.4 mg/dL, with an estimated clearance of 63 mL/min. In patients with cancer, should low-molecular-weight heparin treatment be dosed according to weight, or adjusted using anti-Xa levels?

Learning Objectives

- Review the evidence for adjusting low-molecular-weight heparin (LMWH) therapy in patients with cancer, using anti-Xa activity levels
- Understand the use of anti-Xa monitoring of LMWH in patients with renal failure

Low-molecular-weight heparin (LMWH) is the recommended anticoagulant therapy for cancer-associated venous thromboembolism (CA-VTE).[1] Randomized trials comparing LMWH with warfarin for treatment of CA-VTE have used weight-based dosing.[2,3] Because patients with cancer have a 3-fold higher risk for recurrent thrombosis and 2-fold higher risk for major hemorrhage compared with patients without cancer,[4] ways to increase efficacy or safety of anticoagulant therapy are desired. Renal insufficiency during chemotherapy can also influence LMWH clearance. In other high-risk populations such as children, LMWH doses are adjusted to maintain therapeutic anti-Xa levels.[5] We completed a systematic review to evaluate the evidence for adjusting LMWH dosing on the basis of anti-Xa activity in adults with CA-VTE.

We searched PubMed, Scopus, and Web of Science, using the MeSH terms "low-molecular-weight heparin and neoplasms" and "anti-Xa," with appropriate synonyms. After removal of duplicates, 79 articles underwent title and abstract review. Twenty-four articles were evaluated for inclusion, including references of review articles identified using Google Scholar. Studies were included if patients with cancer were treated with LMWH adjusted to maintain therapeutic anti-Xa levels. One randomized trial,[6] 1 retrospective cohort,[7] and 4 case series[8] or case reports[9-11] were included in the analysis.

Several studies reported bleeding and thrombotic outcomes of patients treated with adjusted-dose LMWH (Table 1). In a randomized trial comparing weight-based vs adjusted-dose dalteparin, 122 patients (58 and 64 patients, respectively) were treated with 10 days of dalteparin therapy for lower-extremity deep vein thrombosis (DVT).[6] The mean dalteparin dose was similar between the groups (100 vs 103 IU/kg/injection), and venographic improvement of the thrombi did not differ. One major and 3 minor hemorrhages occurred in patients treated with weight-based dosing compared with 3 minor hemorrhages in patients receiving anti-Xa adjusted dosing. No recurrent DVT occurred. A pulmonary embolism was suspected in 1 patient in the weight-based group and 2 patients in the adjusted-dose group. The bleeding and thrombotic complications did not statistically differ between patients treated with weight-based or anti-Xa adjusted LMWH. In 3 case reports, adjusted-dose LMWH was given because of a bleeding complication,[11] recurrent thrombosis,[9] or resistance to unfractionated heparin.[10] No subsequent bleeding or thrombosis occurred. Overall, 3 case reports offer anecdotal evidence for anti-Xa monitoring in patients with cancer who have experienced complications, but a randomized study did not show benefit of anti-Xa adjusted therapy.

Two studies included in the review reported whether anti-Xa monitoring affected management. In a case series of patients with cancer with recurrent thrombosis despite oral anticoagulation, 6 of 7 patients required a dose reduction in LMWH to maintain therapeutic levels.[8] A larger retrospective review suggested that anti-Xa monitoring was less useful.[7] Only 56% of patients had anti-Xa levels checked at the appropriate time, and management was changed in 12% of patients (19/157). Therefore, available evidence suggests anti-Xa testing does not often change dosing of LMWH in patients with cancer.

Because of the prolonged LMWH therapy, oncologists may also be concerned about accumulation of LMWH over time. In 24 patients treated in the CLOT trial, anti-Xa levels were available at week 1 and week 4. There was no statistically significant difference in mean anti-Xa levels at week 1 and week 4 (1.11 [range, 0.6-1.88] and 1.03 [range, 0.54-1.70], respectively; $P = .133$).[12] Anti-Xa levels were also examined in a randomized trial of enoxaparin vs enoxaparin/warfarin therapy (15% of patients had cancer). In the 20 patients randomly assigned to enoxaparin, there was no significant difference in anti-Xa levels over time. There also was no correlation between anti-Xa activity and renal function, although all patients had a creatinine clearance higher than 30 mL/min.[13] Current literature does not suggest that LMWH accumulates over time.

Conflict-of-interest disclosure: L.B.K. declares no competing financial interests. M.S. has received research funding from Janssen, Portola, Roche, and PCORI and has consulted for Bio2Medical, Janssen, CSL Behring, and Merck.

Off-label drug use: None disclosed.

Table 1. Management and outcomes of patients with cancer treated with LMWH adjusted by anti-Xa levels

Manuscript	Patients with cancer (n, %)	Medication	Therapeutic range	Reason for monitoring	Recurrent thrombosis	Bleeding
Alhenc-Gelas et al[6]	4/64 (6%)	Dalteparin	0.5-1 IU/mL	Randomization	2/64 (3%)	3/64 minor (5%)
Busby et al[11]	1/1 (100%)	Enoxaparin	0.5-1.1 IU/mL	Bleeding	0/0 (0%)	0/0 (0%)
Cunningham et al[9]	1/1 (100%)	Enoxaparin	1 IU/mL	Recurrent thrombosis	0/0 (0%)	0/0 (0%)
Krajewski et al[10]	1/1 (100%)	Enoxaparin	0.5-1 IU/mL	Heparin Resistance	0/0 (0%)	0/0 (0%)

Despite the elevated risks for bleeding and thrombosis in patients with cancer, there is insufficient evidence to recommend routine monitoring and adjusting LMWH on the basis of anti-Xa activity (grade 2C). However, a previous meta-analysis showed elevated anti-Xa levels and increased risk of major bleeding in patients with renal insufficiency treated with LMWH (5% major bleeding in patients with creatinine clearance 30 mL/min or lower vs 2.4% major bleeding in patients with creatinine clearance higher than 30 mL/min; odds ratio, 2.25; 95% confidence interval, 1.19-4.27).[14] In the setting of severe renal impairment (creatinine clearance of 30 mL/min or less), we suggest anti-Xa monitoring if LMWH is prescribed (grade 2B). Adjusted doses of enoxaparin can be considered for patients with an estimated creatinine clearance between 20 and 30 mL/min.[15] Use of unfractionated heparin or vitamin K antagonist treatment are recommended for patients with more severe renal impairment.[15] Future investigation should evaluate the use of anti-Xa monitoring in patients who have experienced bleeding or thrombotic complications while receiving weight-based LMWH therapy.

Case summary

Treatment with enoxaparin 1 mg/kg every 12 hours was started. The patient presented 4 weeks later with worsening renal function (estimated creatinine clearance, 30 mL/min) and a large back and flank hematoma. After stabilization of his hemoglobin and kidney function, enoxaparin was resumed with a 25% dose reduction. Serial peak anti-Xa levels varied between 0.7 and 0.9 units/mL. The patient has not experienced further bleeding or thrombotic complications.

Correspondence

Lisa Baumann Kreuziger, BloodCenter of Wisconsin; Division of Hematology and Oncology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226; e-mail: lbk@bcw.edu.

References

1. Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012; 141(suppl 2):e419S-e494S.
2. Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (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(2):146-153.
3. Lee AY, Kamphuisen PW, Meyer G, et al; CATCH Investigators. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA*. 2015; 314(7):677-686.
4. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100(10):3484-3488.
5. Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK; American College of Chest Physicians. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012; 141(suppl 2):e737S-e801S.
6. Alhenc-Gelas M, Jestin-Le Guernic C, Vitoux JF, Kher A, Aiach M, Fiessinger JN; Fragmin-Study Group. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis. *Thromb Haemost*. 1994;71(6):698-702.
7. Yentz S, Onwuemene OA, Stein BL, Cull EH, McMahon B. Clinical Use of Anti-Xa Monitoring in Malignancy-Associated Thrombosis. *Thrombosis*. 2015;2015:126975.
8. Naqvi BH, Kapur D, Tjan-Wettstein V, Hickey A, Wallace D. Monitoring antix a levels in cancer patients while on enoxaparin for anticoagulation after failing oral anticoagulation (OAC) [abstract]. *Blood*. 2000;96(11 PART II):100b.
9. Cunningham MS, Gilmore R, O'Donnell D, O'Donnell JS. Management of refractory venous thrombosis associated with malignancy using a supra-therapeutic enoxaparin regimen. *Ir J Med Sci*. 2009;178(3):339-341.
10. Krajewski KC, Smith K, Conwall K, Krajewski MP Jr. Achievement of therapeutic anti-Xa levels in a proven heparin-resistant patient through the use of nontraditional high-dose enoxaparin. *Ann Pharmacother*. 2015; 49(1):130-134.
11. Busby LT, Weyman A, Rodgers GM. Excessive anticoagulation in patients with mild renal insufficiency receiving long-term therapeutic enoxaparin. *Am J Hematol*. 2001;67(1):54-56.
12. Kovacs MJ, Levine MN, Keeney M, Mackinnon KM, Lee AY. Anti-Xa effect of a low molecular weight heparin (dalteparin) does not accumulate in extended duration therapy for venous thromboembolism in cancer patients. *Thromb Haemost*. 2005;93(6):1185-1188.
13. Kucher N, Quiroz R, McKean S, Sasahara AA, Goldhaber SZ. Extended enoxaparin monotherapy for acute symptomatic pulmonary embolism. *Vasc Med*. 2005;10(4):251-256.
14. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144(9):673-684.
15. Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. *Ann Pharmacother*. 2009;43(6):1064-1083.