Dalteparin reduced recurrent venous thromboembolism more than oral anticoagulation in patients with cancer

Lee AY, Levine MN, Baker RI, et al. **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.

QUESTION

In patients with cancer and acute venous thromboembolism (VTE), is low-molecular-weight heparin (LMWH) (dalteparin) more effective than an oral anticoagulant in reducing recurrent VTE?

DESIGN

Randomized (allocation concealed*), blinded (monitoring committee),* controlled trial with 6-month follow-up (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer [CLOT]).

SETTING

48 clinical centers in Canada, Australia, New Zealand, the United States, Italy, the Netherlands, Spain, and the United Kingdom.

PATIENTS

676 patients (mean age 63 y, 51% women) who had active cancer (other than skin cancer) and symptomatic proximal deep venous thrombosis (DVT), pulmonary embolism, or both. Exclusion criteria were weight ≤ 40 kg, Eastern Cooperative Oncology Group performance status score of 3 or 4, therapeutic doses of heparin for ≥ 48 hours before randomization, receipt of anticoagulant therapy, active bleeding in the past 2 weeks, conditions associated with serious bleeding, platelet count < 75 000 mm^3, contraindication to heparin or contrast medium, creatinine level ≥ 3 times the upper limit of normal, or pregnancy. Follow-up was 99.4%.

INTERVENTION

Patients were allocated to dalteparin, 200 IU/kg of body weight (maximal daily dose 18 000 IU) once daily for the first month and 150 IU/kg once daily for the remaining 5 months (n = 336), or to dalteparin, 200 IU/kg for 5 to 7 days, and a coumarin derivative (warfarin or acenocoumarol) adjusted to reach a target international normalized ratio (INR) of 2.5 for 6 months (n = 336).

MAIN OUTCOME MEASURES

Symptomatic, recurrent DVT; pulmonary embolism; or both. Secondary outcomes included major bleeding, any bleeding, and death.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients who received dalteparin had an episode of DVT, pulmonary embolism, or both than did those who received oral anticoagulant therapy (Table). Dalteparin and oral anticoagulant groups did not differ for major (6% vs 4%, P = 0.27) or any bleeding (14% vs 19%, P = 0.09) or for mortality (39% vs 41%, P = 0.53).

CONCLUSION

In patients with cancer and acute venous thromboembolism, treatment with low-molecular-weight heparin lowered the risk for recurrent thromboembolism more than oral anticoagulant therapy.

Source of funding: Pharmacia.

For correspondence: Dr. M.N. Levine, Hamilton Health Sciences, Hamilton, Ontario, Canada. E-mail mlevine@mcmaster.ca.

*See Glossary.

Low-molecular-weight heparin (dalteparin) vs oral anticoagulation for acute venous thromboembolism at 6 months†

Outcomes	Dalteparin	Oral anticoagulation	RRR (95% CI)	NNT (CI)
Recurrent DVT, PE, or both	9%	17%	50% (21 to 68)	12 (9 to 28)

†DVT = deep venous thrombosis; PE = pulmonary embolism. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article using Cox proportional-hazards model.

COMMENTARY

In patients with cancer and VTE, long-term warfarin therapy is challenging because of increased bleeding risk caused by thrombocytopenia or brain involvement, potential warfarin-drug interactions, and limited venous access for INR monitoring. Furthermore, cancer patients spend less time (43.3%) within the target INR range of 2.0 to 3.0 than noncancer patients (56.9%) (1) and are at higher risk for recurrent VTE with an INR ≤ 2.0 than noncancer patients (2). Finally, recurrent VTE can occur despite a therapeutic INR (1). Thus, long-term LMWH therapy has been considered as an alternative to warfarin because it provides a predictable therapeutic anticoagulant effect and does not require laboratory monitoring.

Lee and colleagues have shown that long-term dalteparin is more efficacious than, and as safe as, oral anticoagulation (INR 2.0 to 3.0) for prevention of recurrent VTE in cancer patients with acute thrombosis. Similarly favorable results in cancer patients with acute VTE have also been recently reported with enoxaparin and tinzaparin (3, 4). The study by Lee and colleagues, however, had a larger sample size and was able to reach statistical significance for LMWH efficacy. The necessity and effect of the mandatory dalteparin dose reduction after 1 month and the mandated dose adjustments based on serial platelet count and creatinine assessments remain unclear. This study and those of other LMWHs support the use of once-daily subcutaneous LMWH in place of oral warfarin in cancer patients with acute VTE in order to minimize VTE recurrence rates.

Steven R. Deitcher, MD
Cleveland Clinic Foundation
Cleveland, Ohio, USA

References

1. **Bona RD, Sivjee KY, Hickey AD, Wallace DM, Wajcs SB.** The efficacy and safety of oral anticoagulation in patients with cancer. Thromb Haemost. 1995;74:1055-8.
2. **Hutten BA, Prins MH, Gent M, et al.** Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000;18:3078-83.
3. **Deitcher SR, Kessler CM, Merli G, et al.** Secondary prevention of venous thromboembolic events (VTE) in patients with active malignancy: a randomized study of enoxaparin sodium alone vs. initial enoxaparin sodium followed by warfarin for a 180-day period. J Thromb Haemost. 2003;1 suppl 1:OC194.
4. **Hull RD, Pineo GF, Mah AF, Brant RF.** A randomized trial evaluating long-term low-molecular-weight heparin therapy for three months versus intravenous heparin followed by warfarin sodium. Blood. 2002;100:148a.