Is Anticoagulation in Patients with Cancer Safer Using Low-Molecular-Weight Heparin?

Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 2002;162:1729–35.

Study Overview

Objective. To determine whether a fixed dose of low-molecular-weight heparin (LMWH) is superior to warfarin sodium for the secondary prevention of venous thromboembolism in patients with cancer and established venous thromboembolism.

Design. Prospective randomized multicenter open-label study.

Setting and participants. The study was conducted at 25 centers in France between April 1995 and March 1999. Patients older than 18 years of age with cancer of any type and pulmonary embolism (PE) and/or deep venous thrombosis (DVT) were enrolled. PE was confirmed by angiography or ventilation-perfusion lung scanning that was scored as high probability or abnormal in the setting of a confirmed DVT. DVT diagnosis was confirmed by venography or compression ultrasonography. Cancer was defined as a solid tumor or hematologic malignancy of any type, active, or in remission but with ongoing antitumor treatment. Exclusion criteria included: history of heparin-induced thrombocytopenia, iodine allergy, pregnancy, fibrinolysis in the previous 72 hours, warfarin use greater than 5 days, major PE with shock, life expectancy less than 3 months, contraindications to anticoagulation, liver or kidney failure (serum creatinine levels > 2 mg/dL), or major surgery planned within 3 months.

Intervention. Prior to randomization, all patients were anticoagulated with unfractionated heparin or LMWH. Enoxaparin was given subcutaneously once daily as a fixed dose of 1.5 mg/kg body weight. Patients randomized to the LMWH group continued to receive this unadjusted dose for 3 months. The warfarin group was given 6 to 10 mg of warfarin initially (with international normalized ratio [INR] adjustments made at the discretion of the local investigator or primary care physician) to achieve an INR between 2.0 and 3.0 for 3 months. In this group, LMWH was given until the INR was at least 2.0 on 2 consecutive days after at least 4 days of enoxaparin.

Main outcome measures. The primary outcome was a combined event of treatment failure defined as major bleeding or recurrent PE or DVT within 3 months. Major bleeding was defined as overt or associated with a decrease in hemoglobin concentration by at least 2.0 g/dL, need for transfusion of at least 2 units of blood, or if bleeding was retroperitoneal, intracranial, intraocular, or associated with death. Secondary outcomes included 3- and 6-month mortality, evolution of the underlying cancer at 6 months, major and minor bleeding, heparin-induced thrombocytopenia, and recurrent thromboembolism during the 6-month period. Analysis was by intent-to-treat using χ^2 or Fisher exact tests and t or Wilcoxon rank sum tests.

Main results. The study was interrupted by an independent steering committee because of slow accrual: 146 eligible patients were enrolled over 4 years. After 8 patients were deemed unevaluable, 71 were randomized to warfarin and 67 to enoxaparin. Baseline characteristics were similar in terms of age; body mass index; percent with isolated DVT (~30%), PE (~13%), or both (57%); and percent who were immobilized, had recent surgery, varicose veins, or congestive heart failure. The warfarin group had slightly more patients with a history of a prior venous thrombotic event (31% versus 19%). Cancer types were varied among all patients. Approximately 50% in each cohort had metastatic disease and most (~73%) were undergoing cancer treatment. Nearly all patients received anticoagulation prior to randomization for a mean of 3 days with either unfractionated heparin (38%) or LMWH (~60%).

15 patients in the warfarin group (21% [95% confidence interval {CI}, 12.3%–32.4%]; $P = 0.09$) experienced one primary outcome event compared with 7 patients receiving enoxaparin (10.5% [95% CI, 4.3%–20.3%]; $P = 0.09$; and relative risk, 2.02 [95% CI, 0.88–4.65]). Other comparisons include: major hemorrhage (12 warfarin versus 5 enoxaparin patients; $P = 0.09$); death from hemorrhage (6 *warfarin* versus 0 *enoxaparin* patients; $P = 0.03$); and death from any cause (17 warfarin versus 8 enoxaparin patients; $P = 0.07$). No difference was seen in terms of progression of underlying cancer or cancer-related mortality at 3 or 6 months. The warfarin patients were in the therapeutic INR range for 41% of the 3-month treatment. Four of 5 patients with major bleeding

during the 3-month period involving the upper gastrointestinal tract occurred in the setting of INR values of 4 or higher.

Conclusion. Warfarin is associated with a higher bleeding rate than LMWH in patients with cancer and venous thromboembolism. Prolonged treatment with LMWH in these patients may be as effective and safer than oral anticoagulants.

Commentary

Venous thromboembolic events are common in patients with cancer, accounting for significant morbidity and mortality. Hypercoagulation associated with malignancy, age, surgical procedures, central venous devices, chemotherapeutics, hormonal therapy, and diminished physical activity probably account for most of this increased incidence. When venous thromboembolism precedes or presents concurrently with a diagnosis of cancer, this suggests a more advanced disease associated with distant metastases and reduced survival [1]. The goal in management is to prevent progression and recurrence while minimizing complications of treatment.

Anticoagulation in patients with cancer can be particularly challenging because of the increased risks of recurrent thromboembolic disease and major bleeding [2]. In a recent retrospective analysis, Hutton et al found increased major bleeding and recurrent venous thromboembolism in patients with cancer given warfarin compared with those without cancer (9.0% versus 2.1% and 27.1% versus 13.3% per patient-year, respectively). Moreover, largely anecdotal evidence has suggested that thrombotic disease in patients with cancer may be inherently more resistant to warfarin and more responsive to heparin. LMWH has emerged as an effective and perhaps safer form of anticoagulation than unfractionated heparin [3], though randomized studies have not proven improved safety when compared with warfarin.

Meyer et al conducted a larger prospective randomized study comparing warfarin and LMWH in patients with cancer and PE and/or DVT looking at rates of recurrent thromboembolic disease or major bleeding over a 3-month period. The results suggest that warfarin is associated with more combined primary events (PE and/or DVT or major bleeding), major bleeding, death from bleeding, and death in general than with enoxaparin. Death from bleeding was the only endpoint to reach statistical significance. No differences were seen in cancer progression or disease-specific mortality.

The study's merits are that it is multicenter, randomized, and prospective, thus reducing potential selection or physician/institutional biases. As well, the groups were well balanced in terms of underlying malignancies and stage—the latter not always specified in trials to date. Unfortunately, patient accrual for this study was poor, resulting in very limited numbers for a study involving 25 centers. In a review of records from 4 of the centers, the authors identified 77% of patients admitted with cancer and DVT and/or PE who were ineligible for enrollment. Thus, it is difficult to know how generalizable these results are to patients with cancer and DVT and/or PE. Also, one point of confusion is why more than 25% of patients were not undergoing cancer treatment despite this being a requirement for eligibility. Additionally, it is unclear why the authors do not specify the rate of recurrent venous thromboembolic disease instead of lumping this and major bleeding events into a combined outcome. Are patients who receive enoxaparin experiencing more venous thromboembolic events but less bleeding?

Despite these criticisms, there is the suggestion that enoxaparin may be a safer choice for anticoagulation in patients with cancer. This result may be partially explained by the fact that patients in the warfarin group were outside of the therapeutic INR range 59% of the 3-month period. Most of the gastrointestinal bleeding seen occurred in the setting of INR values of 4 or above. Yet in Hutton's retrospective analysis, interestingly, the major bleeding occurred when INR values were 2 or below [2]. So, it is unclear whether fine tuning or more compulsive management will lead to less bleeding. Finally, it is worth considering that the available LMWH formulations are not identical and clinical use should be based on evidence for the preparation in question. Daily injections are less than ideal for patients who already struggle to live with some degree of normalcy and comfort.

Applications for Clinical Practice

Enoxaparin appears to be at least as safe as warfarin for patients with cancer and DVT and/or PE. The absence of frequent laboratory testing and dose adjustments make treatment easier for physicians and (hopefully) for many patients. More often than not, these patients should remain on anticoagulation indefinitely, though data in this setting are limited beyond 3 to 6 months. Whether these results apply to other LMWH preparations remains to be seen.

–Review by David R. Spigel, MD

References

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