Study Overview

**Objective.** To examine the effect of low-molecular-weight heparin (LMWH) on survival in patients with advanced malignancy without venous thromboembolism (VTE).

**Design.** Prospective, randomized, double-blind trial.

**Setting and participants.** Patients with metastasized or locally advanced solid tumors were randomized to a 6-week course of subcutaneous nadroparin twice daily (0.4 mL for those < 50 kg, 0.6 mL for those between 50 kg and 70 kg, and 0.8 mL for those > 70 kg) during the initial 14 days of treatment and once daily thereafter for another 4 weeks or placebo. Patients were excluded if they had an indication for anticoagulation or were receiving treatment with resulting thrombocytopenia < 50,000/µL. After treatment ended, a standardized questionnaire was used to obtain information about survival and additional therapy.

**Main outcome measures.** The primary endpoint was death as a result of any cause based on time from randomization. Safety outcomes were major bleeding (clinically overt episodes associated with a decrease in hemoglobin > 2 g/dL that led to transfusion of ≥ 2 U of blood or that were located in the retroperitoneal or intracranial area) and nonmajor bleeding. The effect of nadroparin was calculated separately for patients with a life expectancy < 6 months and > 6 months at enrollment and for those receiving or not receiving concomitant chemotherapy.

**Main results.** 302 patients were enrolled (nadroparin group = 148 patients; placebo group = 154 patients), with a mean follow-up of 1 year. Baseline characteristics were well-balanced between arms, with the exception of more breast cancer and less colorectal and cervical cancers among nadroparin recipients. In the intention-to-treat analysis, the overall hazard ratio (HR) of mortality was 0.75 (95% confidence interval [CI], 0.59–0.96), with a median survival of 8.0 months in the nadroparin group versus 6.6 months in the placebo group. When adjusted for life expectancy, performance status, concomitant treatment, and cancer type/histology, the treatment effect remained statistically significant (HR, 0.76 [95% CI, 0.58–0.99]). Major bleeding occurred in 5 (3%) nadroparin-treated patients and in 1 (1%) of the placebo recipients (P = 0.12). In the a priori specified subgroup of patients with a life expectancy of 6 months or more at enrollment, the HR was 0.64 (95% CI, 0.45–0.90) with a median survival of 15.4 in the nadroparin group and 9.4 months in the placebo group. For patients with a shorter life expectancy, the HR was 0.88 (95% CI, 0.62–1.25).

**Conclusion.** LMWH favorably influenced survival in patients with advanced cancer.

**Commentary.** LMWH is considered optimal anticoagulation in patients with cancer and VTE [1]. Its role in patients with cancer without VTE is unknown; however, subset analyses suggest LMWH may provide benefits independent of VTE prevention [2]. Some have speculated that these agents play important roles in directly inhibiting tumor proliferation and metastases, perhaps through inhibitory effects on the clotting system and angiogenesis.

Klerk and colleagues conducted a prospective randomized trial comparing LMWH (nadroparin) with placebo in patients with advanced malignancies. The results were provocative in that LMWH was associated with improvements in overall survival after minimal exposure (6 weeks) and no increased adverse events. Randomization contributed to balanced arms, although there were more patients with breast cancer and fewer with colon and cervical cancer in the LMWH arm. It is conceivable that this disparity, in addition to potential disparities in systemic therapies and schedules, accounted for the findings. Importantly, the authors adjusted for several confounding factors without diminishing the benefits attributable to LMWH. One other explanation for the survival advantage for LMWH could be its preventative role in VTE disease in patients at high risk for fatal pulmonary embolic events. However, this explanation is difficult to believe because patients were exposed to LMWH for only a brief period in their overall course. Any protective benefits for VTE beyond the treatment period would be
unusual and uncommon in clinical practice.

In the end, this study raises more questions than it answers. For example, is this effect limited only to nadroparin, LMWH, or does it apply to all anticoagulants? Is there greater benefit for longer exposure, different dosing, intermittent scheduling, specific tumor types, or concurrent chemotherapies? These questions will hopefully begin to be addressed in prospective trials as new LMWH agents continue to become available.

**Applications for Clinical Practice**

LMWH is currently indicated for the management of thromboembolic disorders in patients with cancer. Use outside of this indication should be limited to investigational use only.

—Review by David R. Spigel, MD

**References**
