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ORIGINAL REPORT

Low Molecular Weight Heparin, Therapy With Dalteparin, and Survival in Advanced Cancer: The Fragmin Advanced Malignancy Outcome Study (FAMOUS)

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ABSTRACT

Purpose
In experimental systems, interference with coagulation can affect tumor biology. Furthermore, it has been suggested that low molecular weight heparin therapy may prolong survival in patients with cancer. The primary aim of this study was to assess survival at 1 year of patients with advanced cancer.

Patients and Methods
Patients with advanced malignancy (N = 385) were randomly assigned to receive either a once-daily subcutaneous injection of dalteparin (5,000 IU), a low molecular weight heparin, or placebo for 1 year.

Results
The Kaplan-Meier survival estimates at 1, 2, and 3 years after randomization for patients receiving dalteparin were 46%, 27%, and 21%, respectively, compared with 41%, 18%, and 12%, respectively, for patients receiving placebo ($P = .19$). In an analysis not specified a priori, survival was examined in a subgroup of patients (dalteparin, n = 55; and placebo, n = 47) who had a better prognosis and who were alive 17 months after randomization. In these patients, Kaplan-Meier survival estimates at 2 and 3 years from randomization were significantly improved for patients receiving dalteparin versus placebo (78% *v* 55% and 60% *v* 36%, respectively, $P = .03$). The rates of symptomatic venous thromboembolism were 2.4% and 3.3% for dalteparin and placebo, respectively, with bleeding rates of 4.7% and 2.7%, respectively.

Conclusion
Dalteparin administration did not significantly improve 1-year survival rates in patients with advanced malignancy. However, the observed improved survival in a subgroup of patients with a better prognosis suggests a potential modifying effect of dalteparin on tumor biology.

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INTRODUCTION

Thrombosis is a complication in patients with solid tumor malignancy,[1] and the heightened risk is secondary to tumor elaboration of tissue factor, a physiologic procoagulant that is responsible for the genesis of a systemic hypercoagulable state.[2] Once activated, coagulation proteases have a profound effect on tumor cell behavior in experimental models,[3] enhancing tumor cell motility, invasion, angiogenesis, and growth. Hence, interference with activated coagulation serine proteases may influence tumor biology.

Heparins are glycosaminoglycans that play a variety of cellular and plasmatic roles.[4,5] In blood coagulation, heparins and their low molecular weight fractions potentiate the activity of antithrombin III, thus inhibiting activated coagulation factors X and II.[6] They also release tissue factor pathway inhibitor, a physiologic inhibitor of the tissue factor pathway,[7,8] and are effective both in the prevention of fatal pulmonary embolism[9] and in deep vein thrombosis treatment.[10]

There has been speculation for many years about the benefits of anticoagulation in cancer patients with regard to prolonga-

tion of survival. Both the oral anticoagulant warfarin[11] and unfractionated heparin[12] have been shown to prolong survival in patients with small-cell lung carcinoma. More recently, retrospective analyses indicate that, compared with those who have received unfractionated heparin, patients with malignant disease who have received low molecular weight heparin for the treatment of their acute deep vein thrombosis seem to experience prolonged survival.[13-15]

We conducted the first randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of chronic administration of low molecular weight heparin in cancer patients without underlying thrombosis. The primary objective was to determine the effect on survival.

PATIENTS AND METHODS

Study Patients

Patients were eligible for inclusion in the study if they were between the ages of 18 and 80 years and had histologically confirmed advanced stage III or IV (locally advanced or metastatic) malignant disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus. Patients were ineligible for randomization if they had an active bleeding disorder, a known hypersensitivity to heparin, or a platelet count below 50,000/μL. Patients were expected to have a survival period of 3 months or greater from time of randomization. No restriction on concomitant use of chemotherapy or radiotherapy was specified. All patients gave written informed consent after institutional ethical committee review and approval of the trial protocol. The study was conducted according to the ethical standards stated in the Helsinki Declaration.

Study Design and Treatment

In this double-blind, placebo-controlled, multicenter study, patients were randomly assigned to receive once-daily subcutaneous injections of either 5,000 IU of the low molecular weight heparin, dalteparin (Fragmin; Pharmacia Corporation), or placebo (0.9% normal saline), each supplied in 0.2-mL prefilled syringes. Therapy was scheduled to last for 1 year or until the patient died, whichever occurred sooner. Patients self-injected the medication on a daily basis and reported their compliance at clinical follow-up. Randomization was performed centrally by computer-generated code.

The primary objective was to assess mortality after 1 year of therapy. Secondary outcomes comprised rates of symptomatic, objectively confirmed venous thromboembolic disease and bleeding complications. Bleeding was defined as major or minor according to standard criteria.[16] Injection-site bruising was recorded separately. The duration of hospitalization episodes was also recorded. Details of previous history of cancer therapy, including chemotherapy, radiotherapy, or surgical interventions, were recorded, and details of chemotherapy and radiotherapy concurrent with study participation were also recorded.

The diagnosis of clinically suspected pulmonary embolism or venous thrombosis was determined according to local practices and was not reviewed centrally. The date and cause of death were recorded and, for patients randomized in the United Kingdom, were further verified against their death certificates. Beyond the period of active trial participation, dates of death were ascertained, when possible, for long-term mortality follow-up.

Assessment of Patients

Patients were due to be seen every 2 months in the outpatient clinic, where a physical review was undertaken. No additional hematologic and biochemical investigations were recorded other than those for the normal management of patients. All patients who gave informed consent and who had at least one injection of study drug or placebo and had at least one follow-up recorded constituted the intent-to-treat population for efficacy and safety analyses.

Although the primary study objective was assessment of survival at 1 year, all patients in the intent-to-treat population, when possible, were observed until death or until censored follow-up. This provided the opportunity to assess the potential long-term biologic effects of treatment administration.

Statistical Analysis

On the basis of the findings of retrospective analyses of the effect of low molecular weight heparin on survival in previous studies of deep vein thrombosis treatment, we aimed to demonstrate a 30% improvement in 1-year survival (a 50% mortality in the placebo group reduced to 35% in the dalteparin group). Given these considerations and with an alpha of 0.05 (one-sided) and a power of 90%, 183 patients were required per treatment group. Survival rates and median survival times were estimated using standard Kaplan-Meier methods and were compared between the treatment groups using the Wilcoxon test. Data in tables are presented as median values with first and third quartiles or as count and percentage, where appropriate. Comparison of treatment groups for thrombosis and bleeding was performed with the Fisher's exact test.

RESULTS

Patients and Treatment

A total of 385 patients were enrolled from 10 centers (seven in the United Kingdom, two in Canada, and one in Italy) between May 1995 and April 2001. Withdrawal of consent before commencing the study medication resulted in 11 patients (six patients in the dalteparin group and five in the placebo group) not being included in the analyses. The remaining 374 patients were analyzed for both efficacy and safety. The median duration of study participation was 10.2 months for dalteparin patients and 9.0 months for placebo patients.

Baseline characteristics of patients in the two groups are listed in Table 1. There were no significant differences in prognostic variables, prior or concomitant treatment characteristics, or distribution of tumor types between the two groups. Primary tumor diagnoses in the dalteparin and placebo groups included breast (21% and 14%, respectively), colorectal (18% and 19%, respectively), ovarian (17% and 15%, respectively), pancreatic (10% and 13%, respectively), and other sites (34% and 39%, respectively). Thirty-four percent of the dalteparin group and 31% of the placebo group received chemotherapy while participating in the study, with 8% receiving radiotherapy in both groups (Table 2).

Table 1. Baseline Characteristics of the Patients

Characteristic	Dalteparin (n = 190) No. of Patients	%	Placebo (n = 184) No. of Patients	%
Age, years				
Median	62.0		60.9	
Interquartile range	53.8-68.4		52.4-69.4	
Sex, female	113	59.5	100	54.3
Primary cancer diagnosis				
Breast	40	21.1	26	14.1
Colorectal	35	18.4	35	19.0
Ovarian	33	17.4	28	15.2
Pancreatic	18	9.5	24	13.0
Other	64	34.0	71	39.0
Histologic grade				
Well	13	7.0	17	9.4
Moderate	61	32.8	57	31.1
Poor	69	37.1	56	31.1
Not known	47	24.7	54	29.3
Stage				
I	3	1.6	1	0.5
II	3	1.6	3	1.6
III	71	37.4	52	28.3
IV	113	59.5	128	69.6
Sites with metastasis				
0	29	15.3	23	12.5
1	101	53.2	117	63.6
2	49	25.8	37	20.1
3	10	5.3	6	3.3
4	1	0.5	1	0.5
Previous treatment				
Chemotherapy	122	64.2	108	58.7
Radiotherapy	78	43.2	77	42.4
Surgery	105	55.3	101	55.4
Hormonal	36	18.9	25	13.6
Other	7	3.7	7	3.8

Survival

Survival estimates for the dalteparin- and placebo-group patients at 1 year after randomization were 46% (95% CI, 39% to 53%) and 41% (95% CI, 34% to 49%), respectively ($P = .19$; Fig 1). The survival rate at 2 years after randomization was 27% (95% CI, 20% to 34%) for patients receiving dalteparin versus 18% (95% CI, 11% to 25%) for patients receiving placebo. At 3 years, the survival rate was 21% (95% CI, 14% to 28%) for patients in the dalteparin group and 12% (95% CI, 5% to 19%) for patients in the placebo group.

Table 2. Concomitant Cancer Therapy

Therapy	Dalteparin No. of Patients	%	Placebo No. of Patients	%
Chemotherapy	64	33.7	57	31.0
Radiotherapy	17	8.4	14	7.6
Surgery	3	1.6	2	1.1

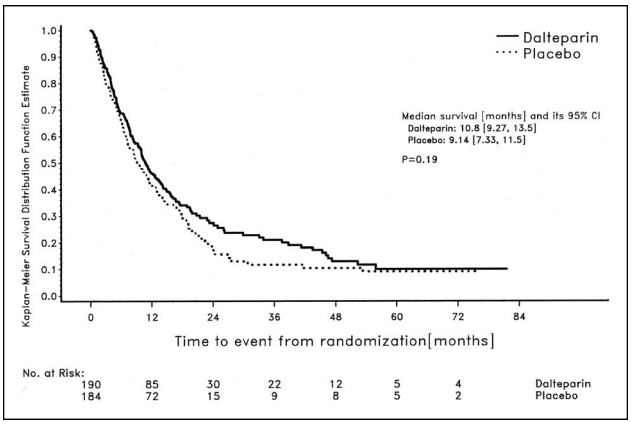

Fig 1. Kaplan-Meier survival curves for all intent-to-treat population patients in the dalteparin and placebo groups.

Analysis of a group of patients (not defined a priori) with a better prognosis and who survived beyond 17 months was undertaken. There were 55 such patients in the dalteparin group and 47 in the placebo group. The Kaplan-Meier survival curves for these patients are shown in Figure 2. There was a significant survival advantage ($P = .03$) for the dalteparin group, with survival estimates at 2 and 3 years after randomization of 78% and 60% for the dalteparin group and 55% and 36% for the placebo group, respectively. The median survival time in the dalteparin group was 43.5 months (95% CI, 33 to 52.3 months) compared with 24.3 months (95% CI, 22.4 to 41.5 months) in the placebo group.

Symptomatic Venous Thromboembolism

The rates of symptomatic thromboembolism were low during the period of study participation, with four patients in the dalteparin group (2.4%) and five patients in the placebo group (3.3%) experiencing an event (Table 3).

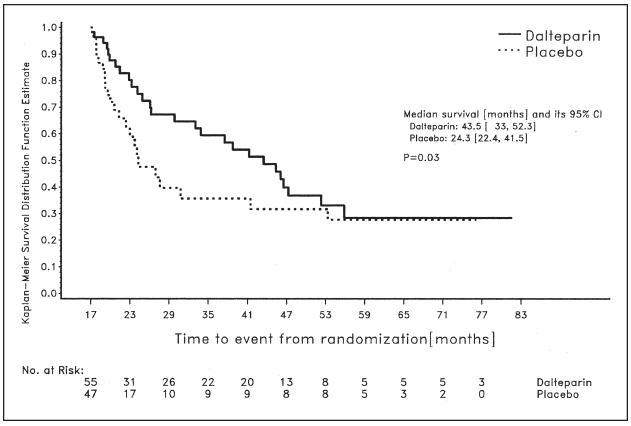

Fig 2. Kaplan-Meier survival curves for the subgroup of patients with a better prognosis who survived beyond 17 months after randomization.

Table 3. Venous Thromboembolism and Bleeding

Event	Dalteparin		Placebo	
	No. of Patients	%	No. of Patients	%
Thrombosis				
Deep vein thrombosis	1	0.6	4	2.6
Pulmonary embolism	2	1.2	0	0.0
Other	1	0.6	1	0.7
Bleeding				
Major	1	0.5	0	0.0
Minor	8	4.2	5	2.7
All	9	4.7	5	2.7

Safety

Overall bleeding rates, shown in Table 3, were 4.7% in the dalteparin group (one major and eight minor bleeds) and 2.7% in the placebo group (five minor bleeds). The one major bleed in the dalteparin group was fatal, although this was not considered to be associated with administration of the study drug.

DISCUSSION

Results of meta-analyses of deep vein thrombosis treatment studies have demonstrated a survival advantage in cancer patients with thrombosis who received low molecular weight heparin compared with unfractionated heparin for initial treatment of their deep vein thrombosis.[13-15] Although this observation is apparently consistent across clinical trials, it is difficult to understand how a short course of low molecular weight heparin could provide such a substantial survival advantage in patients with malignant disease. One plausible explanation for the observed survival advantage with low molecular weight heparin could have been a reduction in silent fatal pulmonary embolic disease. Information on important prognostic variables that might influence outcome from cancer were not recorded in the deep vein thrombosis treatment trials included in the meta-analyses. The only way to determine whether chronic administration of low molecular weight heparin could indeed provide a survival benefit for patients with malignant disease was to undertake a prospective, randomized, controlled trial in patients without underlying thrombosis at the time of randomization.

Our trial has failed to detect a difference, in terms of survival at 1 year from randomization, in patients with advanced malignant disease who received dalteparin versus placebo injections. There are a number of possible explanations for such a finding, including the fact that the study was underpowered to detect significance in the 5% absolute reduction in mortality in favor of the low molecular weight heparin group, as demonstrated in this trial. In addition, there was a high early mortality rate in patients with advanced cancer who were randomized to the trial. These patients, who had a relatively short life span from randomization, may not have been able to benefit from low molecular weight heparin therapy because they died within days or weeks of randomization. It is also possible that low molecular weight heparin therapy may manifest its benefits only in patients with less advanced disease or in patients with a less aggressive biology early in the natural course of their disease.

To test these hypotheses, a posthoc analysis was undertaken in a group of patients with a better prognosis who survived beyond 17 months from randomization. In this subgroup of patients with a more indolent disease, there was a statistically significant difference in survival in favor of those patients randomly assigned to receive low molecular weight heparin. We recognize the limitations of this approach, but nonetheless, the observation of an improved survival in patients with advanced metastatic disease secondary to administration of low molecular weight heparin should encourage further studies in this area.

In this posthoc analysis, the pattern of survival in the dalteparin and placebo groups suggests a potential tumor biology–modifying effect of dalteparin administration. Dalteparin may produce such a biologic effect through inhibition of the activated coagulation proteases that interact with specific protease receptors expressed on tumor cells, inducing gene upregulation and changing physiologic behavior.[3,17,18] Schulman and Lindmarker[19] have also demonstrated an effect of long-term anticoagulant therapy on tumor biology. Patients who received warfarin for 6 months, rather than 6 weeks, for prevention of recurrent venous thromboembolism had a lower incidence of cancer for up to 6 years afterwards.[19]

Heparins may also affect tumor and endothelial cells directly,[20-22] modifying the tumor angiogenic response. Studies have demonstrated a benefit in terms of long-term survival after pelvic surgery for malignant disease in patients who received a short course of in-hospital prophylaxis in the perioperative period.[23] Again, the benefit was seen some time after low molecular weight heparin administration, but in this case, the mechanism may have been interference with tumor cell metastatic seeding at the time of surgery.[24]

There were no significant differences in bleeding complications between the two groups in our study. Dalteparin was given without routine monitoring of anti-Xa activity or platelet levels, suggesting that dalteparin therapy at this dose (5,000 IU, once daily) is safe in the cancer population.

Rates of clinical venous thromboembolism were low in this study. There are few data on the rates of venous thromboembolism in nonsurgical cancer patients, although it is assumed that, in general, they are high.[25] However, in other prospective trials where anticoagulant prophylaxis has been evaluated in cancer patients receiving chemotherapy, rates were lower than expected.[26]

In conclusion, this trial has demonstrated the feasibility and safety of long-term administration of the low molecular weight heparin dalteparin in patients with advanced

cancer. Further evaluation of low molecular weight heparin in appropriately designed trials to assess its potential tumor biology–modifying effects is warranted.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Ajay K. Kakkar, Pfizer. Received more than $2,000 a year from a company for either of the last 2 years: Ajay K. Kakkar, Pfizer.

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