Cancer, thrombosis and low-molecular-weight heparins
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CHAPTER 14

The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy.


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Abstract

Purpose
Studies in cancer patients with venous thromboembolism suggested that low molecular weight heparin may prolong survival. In a double-blind study, we evaluated the effect of low molecular weight heparin on survival in patients with advanced malignancy without venous thromboembolism.

Methods
Patients with metastasized or locally advanced solid tumors were randomly assigned to receive a 6-week course of subcutaneous nadroparin or placebo. The primary efficacy analysis was based on time from random assignment to death. The primary safety outcome was major bleeding.

Results
In total, 148 patients were allocated to nadroparin and 154 patients were allocated to placebo. Mean follow-up was 1 year. In the intention-to-treat analysis the overall hazard ratio of mortality was 0.75 (95% CI, 0.59 to 0.96) with a median survival of 8.0 months in the nadroparin recipients versus 6.6 months in the placebo group. After adjustment for potential confounders, the treatment effect remained statistically significant. Major bleeding occurred in five (3%) of nadroparin-treated patients and in one (1%) of the placebo recipients (P .12).

In the a priori specified subgroup of patients with a life expectancy of 6 months or more at enrollment, the hazard ratio was 0.64 (95% CI, 0.45 to 0.90) with a median survival of 15.4 and 9.4 months, respectively. For patients with a shorter life expectancy, the hazard ratio was 0.88 (95% CI, 0.62 to 1.25).

Conclusion
A brief course of subcutaneous low molecular weight heparin favourably influences the survival in patients with advanced malignancy and deserves additional clinical evaluation.

Introduction
Tumor-mediated activation of the hemostatic system has been implicated in both the formation of tumor stroma and the promotion of hematogenous metastasis (1,2). Therefore, it has been postulated that antithrombotic agents, such as vitamin K antagonists, heparins, and platelet inhibitors, may affect progression of malignancy. In the last decades, the potential antitumor effects of these agents have been investigated in a number of clinical studies (3-6). Although some showed a favourable trend in survival, the aggregate data were inconclusive (7,8). In 1992, Prandoni et al (9) evaluated a low-molecular-weight derivative of heparin, nadroparin, in patients with proven deep vein thrombosis. Unexpectedly, they found an important reduction in mortality in the subgroup of patients with cancer at enrollment who were randomly allocated to receive low molecular weight heparin (3-month mortality of one of 15 (7%) v six of 18 (33%). Subsequently, this effect was confirmed by a systematic review of nine studies dealing with the initial treatment of venous thromboembolism (10). The odds ratio for the 3-month mortality was 0.61 (95% CI, 0.40 to 0.93) in favour of low-molecular-weight heparin. Moreover, this analysis revealed that the mortality reduction was present in various subtypes of malignancy, was not the result of differences in death related to venous thromboembolism more bleedings, and was not altered after adjustment for several prognostic variables. Although these results are derived from a retrospective analysis of studies that did not have the intention to study cancer mortality, they suggest that low molecular weight heparin may have direct anticancer activity. Accordingly, to test this hypothesis, we performed double-blind, placebo-controlled study to evaluate the potential effect of low molecular weight heparin on survival in patients with advanced malignant disease who had no venous thromboembolism.
Methods

Study Population

Adult patients with histologically documented solid malignant tumors that could not be treated curatively were potentially eligible for this study. Patients were excluded if, based on the clinical judgment of the treating physician, they had a life expectancy of less than 1 month, had an indication for anticoagulant treatment (for example, mechanic heart valves, previous venous thromboembolism, or atrial fibrillation), or had a contraindication for low molecular weight heparin. In addition, patients were excluded if they would receive radiotherapy or chemotherapy leading to thrombocytopenia (50,000/L), or were pregnant. Eligible patients were asked for written informed consent. Information collected at baseline included WHO performance status, and type, histology, stage, and duration of cancer. Moreover, before random assignment, the physician’s assessment of life expectancy was recorded (6 v 6 months). This assessment was based on clinical judgment, taking into account prognostic variables such as the stage of the cancer, the performance status of the patient, previous antineoplastic treatment, previous response to treatment, and progression rate. The study was approved by the respective institutional review boards of each participating center. The study treatment was provided by Sanofi-Synthelabo (Paris, France). Protocol design, data collection, and analysis were solely the responsibility of the authors.

Treatment Regimens

Sequentially numbered boxes of syringes with nadroparin or placebo were prepared using a central computer-generated randomization schedule, stratified for body weight with blocks of four. Prefilled syringes containing a fixed volume of nadroparin (9,500 antifactor Xa U/mL) (11) or placebo were provided according to patient’s weight: 0.4 mL for those weighing less than 50 kg, 0.6 mL for those weighing between 50 and 70 kg, and 0.8 mL for those weighing more than 70 kg. Study treatment was to be administered subcutaneously twice daily during the initial 14 days of treatment and once daily thereafter for another 4 weeks. This regimen was selected to mimic the exposure to therapeutic doses of low-molecular-weight heparin that had been associated with survival benefit in previous studies. The continuation with half the initial dose was to maximize the duration of exposure to low-molecular-weight heparin while minimizing the associated risk of bleeding. Patients or family members were instructed how to inject the study treatment, but home care or equivalent nursing services were arranged when indicated. Platelet counts were performed once between 7 to 14 days and at the end of treatment. In the event of severe thrombocytopenia (50,000/L), treatment was stopped and tests for heparin-associated antiplatelet antibodies were performed.

Follow-Up

Patients were seen at 7 to 14 days after inclusion and at the end of study treatment. During these visits special attention was paid to bleeding. Patients were instructed to report to the study center immediately if abnormal bleeding occurred. For the period after study treatment was ended, a standardized questionnaire was used to obtain information about survival and additional antineoplastic therapy. If necessary, the treating physician, the family doctor, or the patient’s chart was consulted. All patients were observed until death or until the end of the study, with a minimum of 3 months of follow-up.

Outcome Measures

The primary end point was death as a result of any cause. Safety outcomes were major and clinically relevant non major bleeding (12). Major bleeding was defined as clinically overt episodes that were associated with a decrease in haemoglobin of more than 2 g/dL, that led to
transfusion of two or more units of blood, or that were located in the retroperitoneal or intracranial area. Overt bleeding episodes that did not meet these criteria but led to medical intervention were considered as clinically relevant.

Statistical Analysis

The calculation of sample size of 150 patients per group was based on an expected cumulative mortality rate of 40% after a mean follow-up of 12 months in the placebo group and a proportional risk reduction of 30% with nadroparin based on the previous studies (10). A two-sided type I error of 0.05 and a power of 80% were used. All primary analyses were performed on an intention-to-treat principle. The primary analysis of survival was based on the time from random assignment to death. Patients alive at the end of follow-up were censored. Survival estimates were calculated according to the Kaplan-Meier method. The effect of nadroparin was calculated using a two-sided log-rank test. Ninety-five percent confidence intervals were calculated when appropriate. The Cox proportional hazards regression model was used to adjust the treatment effect for potential confounding variables, such as life expectancy (6 v 6 months), WHO performance status (1 or less, 2, 3 or more) concomitant treatment (chemotherapy, radiotherapy, hormonal therapy, other antineoplastic treatment), type of cancer (breast, colorectal, cervical, or other), and histology (adenocarcinoma, squamous, other). The effect of nadroparin was calculated separately for patients with a life expectancy of less than 6 months or 6 months at enrollment, and for those receiving concomitant chemotherapy or not. In addition, statistical tests for interactions of these variables with treatment effect were performed. Finally, for types of cancer and groups of histology with more than 50 patients, the effect of nadroparin was calculated separately. The incidences of major bleeding and all clinically relevant bleeding were compared between the groups using a two-sided Fisher's exact test.

Results

Population

Between May 1996 and February 2003, a total of 302 patients were enrolled onto this study. Of these, 148 patients were allocated to nadroparin and 154 patients were allocated to placebo. Most of the baseline characteristics of the patients were well balanced between the two groups. However, breast cancer was more frequent among nadroparin recipients, whereas colorectal and cervical cancers were seen more often among the placebo recipients. A small proportion of patients did not have metastatic disease. The types of locally advanced disease in this group included hepato-cellular, esophageal, and pancreatic cancer. Follow-Up and Anticancer Treatment. The mean duration of follow-up was considered for 12 months and no patients were lost to follow-up. The great majority of patients injected themselves. Reasons for premature discontinuation of study treatment and use of concomitant antineoplastic therapy are listed in Table 3. Chemotherapy was more frequently administered during the period of study treatment in patients receiving placebo, whereas radiotherapy was more frequently given to patients receiving nadroparin.

Mortality

At 6 months the survival was 61% in the nadroparin group versus 56% in the placebo group. For 12 months these estimates were 39% v 27%, and for 24 months these estimates were 21% v 11% (Fig 1). In the intention-to-treat population, the median survival was 8.0 months in the nadroparin group and 6.6 months in the placebo group. The hazard ratio of mortality was 0.75 (95% CI, 0.59 to 0.96; P.021) in favour of the nadroparin group. When adjusted for life expectancy, WHO performance status, concomitant treatment, and type and histology of
cancer, the treatment effect remained statistically significant (hazard ratio, 0.76; 95% CI, 0.58 to 0.99).

The effect of nadroparin was more pronounced in patients with an estimated life expectancy of 6 months or more at enrollment (hazard ratio, 0.64; 95% CI, 0.45 to 0.90; P < .010; Fig 2) than in those with a life expectancy of less than 6 months (hazard ratio, 0.88; 95% CI, 0.62 to 1.25), although the test for the interaction between life expectancy and treatment effect was not statistically significant. The median survival of patients whose life expectancy was more than 6 months was 15.4 and 9.4 months for the nadroparin and the placebo group, respectively. The effect of nadroparin was similar in patients who received concomitant treatment with chemotherapy and those who did not (hazard ratio, 0.68; 95% CI, 0.42 to 1.12; hazard ratio, 0.75; 95% CI, 0.57 to 1.00). In patients who had adenocarcinoma, the use of nadroparin was associated with a hazard ratio of 0.68 (95% CI, 0.51 to 0.91). For the two largest tumor subgroups, colorectal and breast cancer, the hazard ratios were 0.83 (95% CI, 0.46 to 1.51) and 0.78 (95% CI, 0.41 to 1.48), respectively. In an on-treatment analysis on the overall population, a hazard ratio of 0.70 was found (95% CI, 0.52 to 0.94).

Safety Outcomes

Major bleeding occurred in five (3%) of nadroparin treated patients and in one (1%) of the placebo recipients (P < .12). None of these events was fatal. The respective rates of all clinically relevant bleeding (major and non major combined) were 7% and 1% (P < .005). Of the bleeding episodes in the nadroparin group, five (three major) were spontaneous bleeds associated with the malignancy, such as a gastrointestinal bleed in a patient with esophageal metastasis of a lung carcinoma, and hematuria in a patient with bladder cancer. One major bleeding episode occurred during an intervention (drainage of ascites). No occurrences of heparin-induced thrombocytopenia were observed.

Discussion

This study shows that a 6-week course of low molecular weight heparin in patients with advanced solid malignancy reduces mortality at 12 and 24 months by 12% and 10%, respectively, and prolongs median survival from 6.6 to 8.0 months. This benefit was maintained after adjustment for potential confounders. Given that the unadjusted and adjusted risk estimates are similar (0.75 v 0.76), the presence of confounding is unlikely. The survival benefit was achieved at the cost of a reasonably low incidence of major bleeding (3%), and a modest discomfort of 6 weeks of daily subcutaneous injections. The number needed to treat to prevent one death at 12 or 24 months is only eight or 10 patients, respectively. Interestingly, in the a priori specified subgroup of those with a life expectancy of at least 6 months at enrollment, the median survival increased from 9.4 to 15.4 months. These improvements in survival with a minimum of side effects compare favourably with other recently introduced treatments for patients with advanced malignancy (13). In an on-treatment analysis, the beneficial effect of low molecular weight heparin on cancer survival was even more pronounced. However, these numbers should be interpreted with caution, given that the large number of patients discontinuing medication because of death may introduce bias (14-16). To our knowledge, this is the first randomized, placebo-controlled study that observed a (modest) survival benefit of a low molecular weight heparin in the study population as a whole. Two other studies (with some important differences in patient selection, dose, and duration of low-molecular-weight heparin) found a clearly improved survival in certain subgroups of patients with a better prognosis (17,18). This observation is consistent with the results obtained in our patients with a life expectancy at entry of at least 6 months, in whom the median survival was improved by half a year. Of course, one has to take into account that this selection was based on clinical judgment.
of the physician only. On the other hand, this enables an integration of various prognostic variables such as progression of the cancer over time, tumor stage, and so on. However, given that in the other studies patients with a better prognosis were redefined differently (patients without metastases and patients who survived for a certain time period after inclusion, respectively), gaining a better understanding about which patient characteristics are associated with a favourable response to low molecular weight heparin is still a challenge. The mechanism through which low molecular weight heparin exerts its anticancer effect remains speculative. Although coagulation proteases and fibrinolytic factors play a significant role in cancer progression (19), it is conceivable that low molecular weight heparin may also have non-anticoagulant properties that can favourably influence the natural history of cancer. Experimental studies have shown that low molecular weight heparin can interfere with angiogenesis, adhesion of cancer cells to vascular endothelium, and invasion (20). In fact, because the beneficial effect of low molecular weight heparin on cancer survival was seen in such a wide variety of cancer types both in the meta-analysis of Hettiarachchi et al (10) and in the present study, this suggests interference with a common underlying mechanism in cancer biology. It is highly unlikely that the observed difference in survival is due to prevention of fatal pulmonary embolism, given that the beneficial effect of low molecular weight heparin remained long after the administration of the study drug had stopped. Several methodological aspects of this study require comment. Although the internal validity of this randomized, double-blind, long-term, follow-up study appears tube adequate, its generalizability might be limited due to several factors. We included approximately 300 patients during a period of several years and have no information on potentially eligible patients who did not participate. Furthermore, study treatment was initiated at various time points in the palliative phase of their malignancy. In addition, it is hard to establish which patients might better benefit from the investigated strategy, given that patients with a wide variety of cancer types and antineoplastic regimens were allowed to enter onto the study. It should, however, be noted that in the earlier studies on treatment of venous thromboembolism, the mortality reduction associated with low molecular weight heparin, as discussed previously, was not limited to a specific group of cancer patients (10). Although the chosen low molecular weight heparin regimen was partly based on the treatment schedules used in the thrombosis studies, it remains to be established which schedule might be associated with the greatest benefit. Nevertheless, the 6-week course of subcutaneous injections was feasible in approximately three fourths of the patients, even when combined with other antineoplastic therapies. Finally, this study evaluated nadroparin, but if we take into account the effect on longevity, which was seen in other studies that evaluated other commercial low molecular weight heparin preparations (17,18), the observed effect does not appear to be specific to this low molecular weight heparin. It remains to be determined whether other heparin derivatives, or even new drugs (such as synthetic pentasaccharides), share this effect as well.

In conclusion, the results of this study indicate that a brief 6-week course of subcutaneous low molecular weight heparin favourably influences the survival in patients with advanced solid malignancy. The potential role of low molecular weight heparin in cancer patients deserves additional clinical evaluation. In particular, these studies should focus on identifying the types and stage of cancer that are most likely to respond to this form of therapy, as well as on optimizing the dose and duration of treatment.

Appendix

The following investigators and institutions participated in the MALT trial: Steering committee: H.R. Buller, C.P.W.Klerk, A.W.A. Lensing, J.M.M.B. Otten, S.M. Smorenburg; Data safety and monitoring board: S. Middeldorp, M.H. Prins; Clinical centers: the Netherlands (220 patients): Academic Medical Center of the University of Amsterdam, Amsterdam—C.P.W. Klerk, A.W.A. Lensing, J.M.M.B. Otten, D.J. Richel, S.M. Smorenburg, G. van Tienhoven; Reinier de Graaf Group, Delft, Delft—M.M.E.M. Bos; Academic Hospital Maastricht, Maastricht—K. Hamulyak, M.R. Nijziel; Hospital Bernhoven, Veghel—L.H. van Hulstefijn; Onze Lieve
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