Randomized Phase III Trial of Low Molecular Weight Heparin Enoxaparin in Addition to Standard Treatment in Small Cell Lung Cancer

the RASTEN Trial

Ek, L; Gezelius, E; Bergman, B; Bendahl, P O; Anderson, H; Sundberg, J; Wallberg, M; Falkmer, U; Verma, S; Belting, M; Swedish Lung Cancer Study Group (SLUSG)

Published in:
Annals of Oncology

DOI (link to publication from Publisher):
10.1093/annonc/mdx716

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 398–404, 2018
doi:10.1093/annonc/mdx716
Published online 2 November 2017

ORIGINAL ARTICLE

Randomized phase III trial of low-molecular-weight heparin enoxaparin in addition to standard treatment in small-cell lung cancer: the RASTEN trial

L. Ek[1], E. Gezelius[2,3], B. Bergman[4], P. O. Bendahl[3], H. Anderson[5], J. Sundberg[2], M. Wallberg[1], U. Falkmer[6], S. Verma[7] & M. Belting[2,3]*, on behalf of the Swedish Lung Cancer Study Group (SLUSG)

Departments of [1]Heart and Lung Disease; [2]Hematology, Radiophysics and Oncology, Skåne University Hospital, Lund; [3]Section of Oncology and Pathology, Department of Clinical Sciences, Lund, Lund University, Lund; [4]Department of Lung Medicine, Sahlgrenska University Hospital, Gothenburg; [5]Section of Cancer Epidemiology, Department of Clinical Sciences, Lund, Lund University, Lund, Sweden; [6]Department of Oncology, University Hospital, Aalborg, Denmark; [7]Department of Oncology, University of Calgary, Calgary, Canada

Correspondence to: Prof. Mattias Belting, Section of Oncology and Pathology, Department of Clinical Sciences, Lund, Lund University, Barngatan 4, SE-221 85 Lund, Sweden. Tel: +46-178549; E-mail: mattias.belting@med.lu.se

Background: Coagulation activation and venous thromboembolism (VTE) are hallmarks of malignant disease and represent a major cause of morbidity and mortality in cancer. Coagulation inhibition with low-molecular-weight heparin (LMWH) may improve survival specifically in small-cell lung cancer (SCLC) patients by preventing VTE and tumor progression; however, randomized trials with well-defined patient populations are needed to obtain conclusive data. The aim of RASTEN was to investigate the survival effect of LMWH enoxaparin in a homogenous population of SCLC patients.

Patients and methods: We carried out a randomized, multicenter, open-label trial to investigate the addition of enoxaparin at a supraprophylactic dose (1 mg/kg) to standard treatment in patients with newly diagnosed SCLC. The primary outcome was overall survival (OS), and secondary outcomes were progression-free survival (PFS), incidence of VTE and hemorrhagic events.

Results: In RASTEN, 390 patients were randomized over an 8-year period (2008–2016), of whom 186 and 191 were included in the final analysis in the LMWH and control arm, respectively. We found no evidence of a difference in OS or PFS by the addition of enoxaparin [hazard ratio (HR), 1.11; 95% confidence interval (CI) 0.89–1.38; $P = 0.36$ and HR, 1.18; 95% CI 0.95–1.46; $P = 0.14$, respectively]. Subgroup analysis of patients with limited and extensive disease did not show reduced mortality by enoxaparin. The incidence of VTE was significantly reduced in the LMWH arm (HR, 0.31; 95% CI 0.11–0.84; $P = 0.02$). Hemorrhagic events were more frequent in the LMWH-treated group but fatal bleedings occurred in both arms.

Conclusion: LMWH enoxaparin in addition to standard therapy did not improve OS in SCLC patients despite being administered at a supraprophylactic dose and despite resulting in a significant reduction in VTE incidence. Addition of LMWH cannot be generally recommended in the management of SCLC patients, and predictive biomarkers of VTE and LMWH-associated bleeding in cancer patients are warranted.

Key words: small-cell lung cancer, low-molecular-weight heparin, venous thromboembolism, enoxaparin, coagulation, randomized phase III trial

Introduction

Lung cancer is the most common type of cancer worldwide, and despite medical advances, mortality is high representing ∼1/5 of cancer-related deaths [1]. SCLC accounts for ∼15% of all lung cancer cases [2] and is characterized by neuroendocrine activity and early metastasis. Although most patients show an initial good treatment response, the prognosis is poor with 5-year survival rates of <10%.

Venous thromboembolism (VTE) is a well-recognized complication in malignancy and a major contributor to cancer-associated mortality and morbidity [3, 4]. Coagulation activation is intimately related to tumor development, which has been

mechanistically linked to the induction of tissue factor (TF), i.e. the main initiator of coagulation [5, 6]. Low-molecular-weight heparin (LMWH) binds to antithrombin-III and potentiates its inhibition of procoagulant factor Xa [7]. Experimental evidence suggests that LMWH has antitumor effects via, e.g. inhibition of angiogenesis and metastasis [8–10]. This has prompted studies to evaluate antitumor effects of heparin in patients, which have provided contradictory results [11]. An early meta-analysis showed a reduced mortality among cancer patients receiving LMWH as treatment of VTE [12], supported by a retrospective analysis of the CLOT study showing that LMWH compared with coumarin-derivative as treatment of VTE significantly reduced 1-year mortality in patients with nonmetastatic disease [13]. Similarly, two randomized trials comparing prophylactic LMWH to placebo in patients with advanced malignancy reported improved survival particularly in patients with a favorable prognosis [14, 15].

Interestingly, several reports suggest a particular survival benefit with anticoagulation therapy in patients with SCLC [16, 17]. In a small randomized clinical trial ($N = 84$), Altinbas et al. showed a median survival of 13 months in the LMWH group compared with 8 months in the control group [16], and Lebeau et al. [17] reported an improved survival of 317 days with the addition of unfractionated heparin as compared with 216 days in patients receiving standard chemotherapy alone. A Cochrane report concluded that among a heterogeneous group of cancer patients with no therapeutic or prophylactic indication for anticoagulation, increased 1-year survival with LMWH was uniquely seen in SCLC patients [18], which was supported by a meta-analysis of nine separate studies [19]. However, a recent randomized trial showed no survival benefit by the addition of LMWH to standard care in a large population of lung cancer patients with mixed histology [20]. Importantly, most of the above studies were carried out with the LMWH dalteparin administered at a prophylactic dose, which may be suboptimal for the tumor-inhibiting effects [10, 14, 16, 20]. Although LMWHs (dalteparin, enoxaparin, and tinzaparin) have similar antithrombotic effects, they have distinct pharmacological properties and may differentiate in their ability to inhibit metastasis [21].

The aim of the RASTEN trial was to investigate whether addition of LMWH enoxaparin at a supraprophylactic dose to standard treatment improves survival rates compared with standard treatment in a homogenous group of SCLC patients.

Patients and methods

Study design

RASTEN is a *r*andomized-phase-III-*s*tudy-of-standard-treatment-with-or-without-the-addition-of-*e*noxaparin in SCLC (ClinicalTrials.gov: NCT00717938), which was initiated and conducted by the Swedish Lung Cancer Study Group. In this international, open-label trial, patients were enrolled at 23 different centers (17 in Sweden, 5 in Canada and 1 in Denmark). Patients were included with histologically or cytologically verified SCLC of all stages, age 18 years or above, World Health Organisation performance status 0–3, platelet count $>100 \times 10^9$/l and standard coagulation parameters within normal ranges. Key exclusion criteria were prior systemic chemotherapy, concomitant anticoagulant treatment except acetylsalicylic acid or clopidogrel, active bleeding or high risk of clinically significant bleeding, pregnancy or lactation, or other known contraindications to enoxaparin. All eligible patients gave written informed consent before study entry. The study was carried out according to the ICH/GCP guidelines and in agreement with the Helsinki declaration and was approved by Läkemedelsverket (MPA) and the local ethics committee, Lund University.

Randomization

Patients were randomized 1 : 1 between a control arm receiving standard treatment and an intervention arm receiving standard treatment with the addition of enoxaparin. Patients were stratified according to performance status, disease stage, age, gender and study center. The randomization procedure was conducted at the Clinical Research Unit at Lund University Hospital, using a computer algorithm.

Treatments

Standard therapy included a platinum compound and a topoisomerase inhibitor administered for four to six cycles according to local guidelines. Radiotherapy was given depending on disease extent and response to chemotherapy, following local protocols. In the intervention arm, enoxaparin was given at 1 mg/kg as daily subcutaneous injections. The study drug was started on day 1 of chemotherapy and continued until the 21st day of the last chemotherapy cycle. To measure compliance, patients were instructed to bring the empty syringe packages to each study visit, and reasons for treatment interruptions were recorded. Anticoagulation at therapeutic or temporary prophylactic dosages was allowed if clinically indicated.

Follow-up

Patients were seen before start of each chemotherapy cycle. After completion of treatment, follow-up was carried out at 8 weekly intervals and included clinical examination and a chest X-ray at a minimum, or according to local guidelines.

End points

The primary end point, overall survival (OS), was defined as the date of randomization to the date of death from any cause. For patients not reported dead, information regarding vital status was confirmed from each study center before data collection cut-off at 4 April 2017, at which point the follow-up was censored for all patients still alive. Secondary outcomes included progression-free survival (PFS) measured from the date of randomization to the date of objective or clinical progression or death from any cause, whichever came first. VTE and hemorrhagic events were graded according to NCI-CTCAE3.0 criteria [22]. VTE diagnosis was made by routine examination according to local protocol. The study treatment was stopped permanently in case of a major hemorrhage, defined as a decrease in hemoglobin >20 g/l or requiring transfusion of two or more units of blood, any intracranial hemorrhage, VTE requiring therapeutic anticoagulation, a persistent decrease in platelets $<50 \times 10^9$ g/l or any other reason at the investigator's discretion.

Statistical analyses

All patients initiating the first treatment cycle were included in the statistical analysis according to intention to treat (ITT). Patients who withdrew from the study were included in the ITT analyses, but their follow-up times were censored at the date of withdrawal of consent.

Assuming exponentially distributed survival times, an accrual period of 78 months and an additional follow-up of 12 months thereafter, 195 patients per arm would be required to have 80% power to detect an increase in one-year survival rate from 35% to 46% in the intervention arm at the alpha level 5% with a two-sided log rank test. Due to a slower inclusion rate than initially expected, the protocol was amended (study protocol version 8.0) and approval from the MPA and ethics

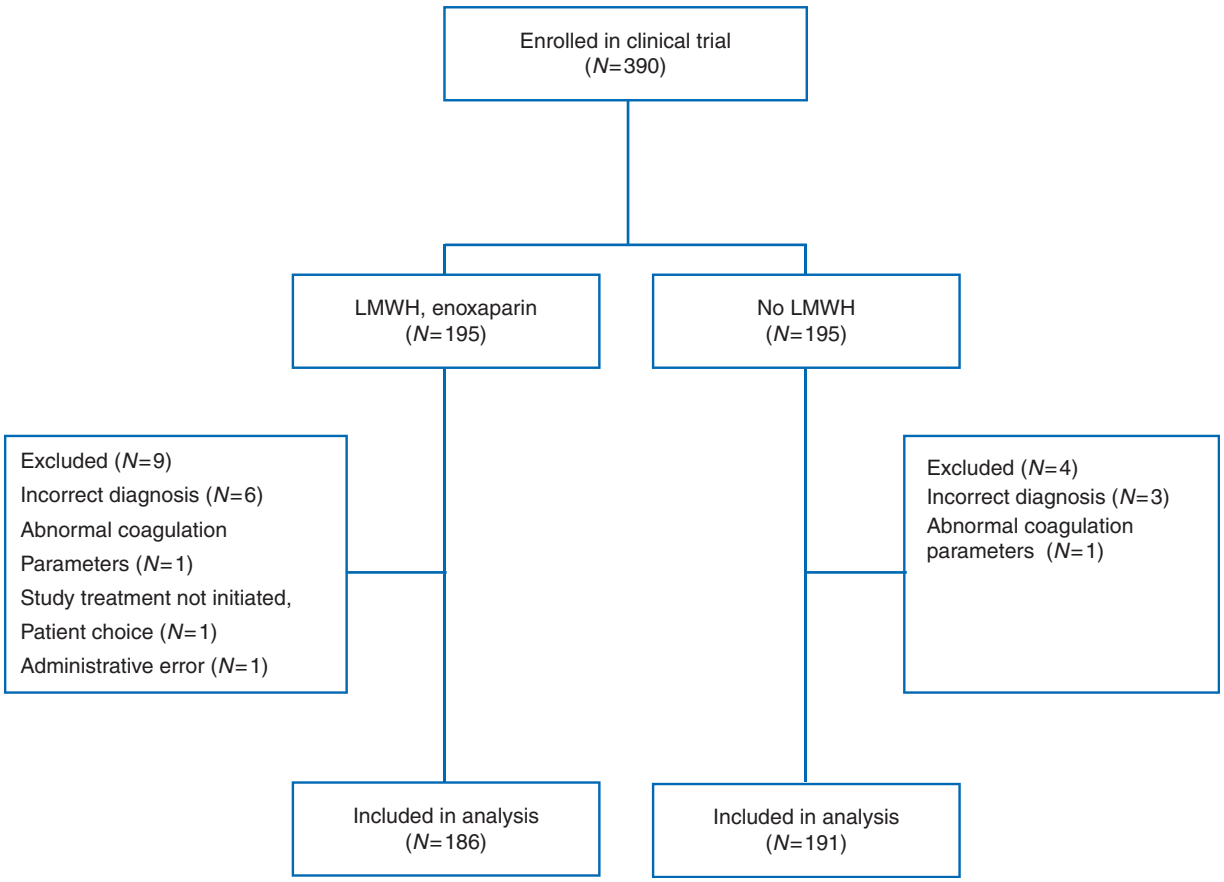

Figure 1. CONSORT diagram of the RASTEN study population.

committee was given to extend the study period. The statistics packages SPSSv22 and STATA14.1 were used for data analysis. Survival was estimated using the Kaplan–Meier method and the log rank test was used to compare the survival curves. Cox regression was used to quantify the effect of treatment on outcome [hazard ratio (HR) with 95% confidence interval (CI)]. The statistical analysis of the primary outcome (OS) was unadjusted, but a complementary multivariable analysis was carried out to improve the precision in the treatment effect measure. Cumulative incidence of first VTE, per treatment group, was calculated using a standard method which accounts for death without VTE as a competing event [23].

Results

Study population

Between July 2008 and March 2016, 390 patients were enrolled with nine cases excluded due to other histology than SCLC and four patients for other reasons (Figure 1). Four cases withdrew consent after initiating treatment and their follow-up times were censored from the withdrawal date. A total of 377 patients were included in the ITT population; 186 in the LMWH enoxaparin arm and 191 in the control arm. Median follow-up was 41 months (interquartile range, 21–81 months) for patients still alive. Baseline characteristics were comparable between both arms (Table 1).

In the LMWH and control groups, respectively, 158 (85%) and 166 (87%) patients completed four or more cycles of chemotherapy. The proportion of patients receiving radiotherapy was similar with the exception of radiation towards metastatic lesions where the control group was overrepresented. Treatment summary is shown in supplementary Table S1, available at *Annals of Oncology* online. Approximately 85% of the patients in the enoxaparin group reported full adherence after each treatment cycle and the temporary cessation of LMWH was on average only 7 days.

Patient outcome

The primary end point, median OS, was 10.6 months in the LMWH group and 11.3 months in the control group (HR, 1.11; 95% CI 0.89–1.38; $P = 0.36$) (Figure 2). Stratification for study center and adjustment for age, gender, disease stage and performance status gave a HR of 1.14 (95% CI 0.91–1.45; $P = 0.26$). The 1-year survival rates were 48% and 47% in the LMWH and control groups, respectively (HR, 0.98; 95% CI 0.74–1.30; $P = 0.92$).

The median OS was 17.8 and 8.6 months in patients with limited disease (LD) and extensive disease (ED), respectively ($P < 0.001$). There were no survival differences between the treatment arms when analyzing the subgroups depending on disease stage (Figure 3). The addition of LMWH had no significant effect on PFS (HR, 1.18; 95% CI 0.95–1.46; $P = 0.14$) (supplementary Figure S1, available at *Annals of Oncology* online).

VTE and hemorrhagic events

VTE and hemorrhagic events are listed in supplementary Table S2, available at *Annals of Oncology* online. The VTE incidence was significantly higher in the control arm where 16 patients (8.4%) developed a VTE compared with 5 (2.7%) in the LMWH group ($P = 0.02$). Two of the control patients developed fatal pulmonary embolization. The cumulative incidence of VTE at 6 months was 2.5% and 8.5% in the LMWH and control arms, respectively (HR, 0.31; 95% CI 0.11–0.84; $P = 0.02$) (Figure 4).

Hemorrhagic events were reported in 27 cases in the LMWH group. However, the majority were considered clinically non-relevant (CTC grades 1–2) [22], whereas three patients suffered fatal pulmonary hemorrhages. In the control group, eight patients experienced hemorrhagic events, including one fatal. The distribution of other adverse events was equal between the treatment arms (supplementary Table S3, available at *Annals of Oncology* online).

Table 1. Baseline characteristics of the study population

	Enoxaparin (*N* = 186)	Control (*N* = 191)
Age, years		
Median ± SD	67 ± 7.9	68 ± 8.5
IQR	62–72	62–73
Gender, *n* (%)		
Female	108 (58)	109 (57)
Male	78 (42)	82 (43)
Performance status, *n* (%)		
0–1	134 (72)	136 (71)
2–3	52 (28)	55 (29)
Disease stage, *n* (%)		
Limited	72 (39)	78 (41)
Extensive	114 (61)	113 (59)
Biochemistry, median (IQR)		
Hemoglobin, g/l	132 (122–146)	134 (123–143)
Leukocyte count, $\times 10^9$/l	9.5 (7.4–12.3)	9.7 (7.6–12.7)
Platelet count, $\times 10^9$/l	353 (274–445)	334 (262–419)
Sodium, mmol/l	138 (135–140)	138 (135–140)
Potassium, mmol/l	4.1 (3.9–4.5)	4.2 (4.0–4.5)
Serum creatinine, µmol/l	65 (57–75)	66 (56–80)

IQR, interquartile range.

Discussion

Studies on the tumor-promoting effects of the coagulation system have provided a strong rationale for further investigations on the role of LMWH in cancer treatment [8–11, 24–25]. However, conflicting results from clinical studies reflect the need for randomized trials with well-defined patient populations to obtain conclusive data. The RASTEN study is, to our knowledge, the largest trial that investigates the survival effect of LMWH in a patient population with a homogenous tumor histology, SCLC, which differs significantly from non-SCLC [26]. Further, this is the only randomized controlled trial that investigates the antitumor effect of LMWH used at a higher, supraprophylactic dose. We found that the addition of enoxaparin to standard therapy does not improve survival in SCLC patients. This was true for patients with LD as well as ED, and in spite of a significant reduction of VTE events.

Aggressive tumors are characterized by poorly perfused areas with hypoxia-induced overexpression of TF and fVIIa [5, 6, 27] that, independently of blood clot formation, can promote tumor progression via activation of protease-activated receptors (PARs) [28]. The lack of an antitumoral effect of LMWH in spite of reduced systemic thrombosis may thus in part be related to poor distribution to the procoagulant, hypoxic tumor niche, or to the inability of LMWH to target coagulation-dependent signaling. LMWH may offer a multitargeted strategy with simultaneous

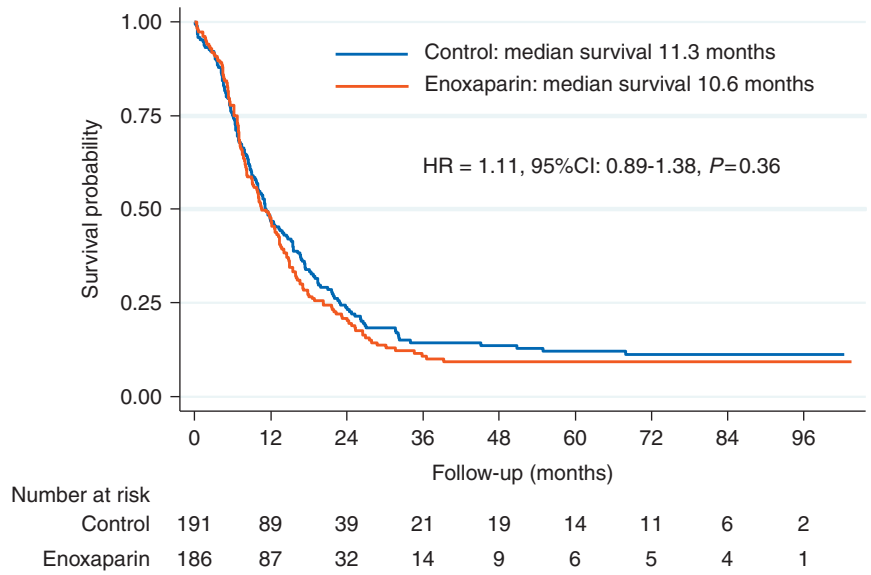

Figure 2. Kaplan–Meier curve of overall survival by treatment arm.

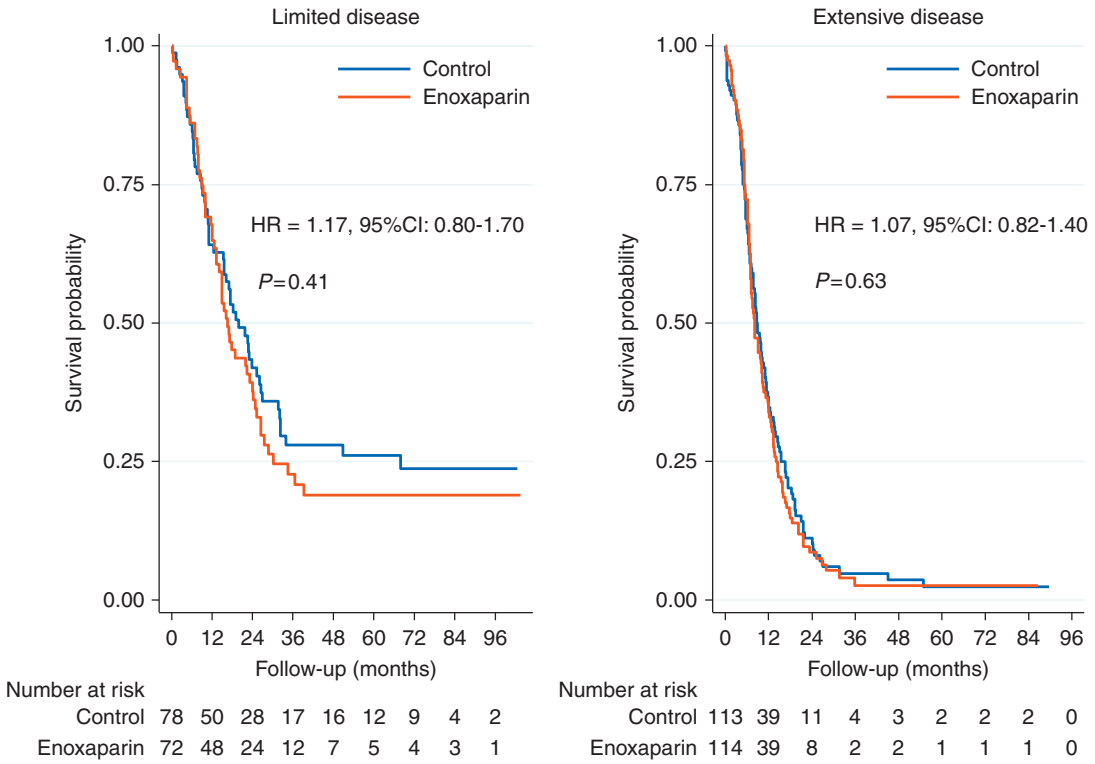

Figure 3. Kaplan–Meier curves of overall survival by disease extent according to treatment arm.

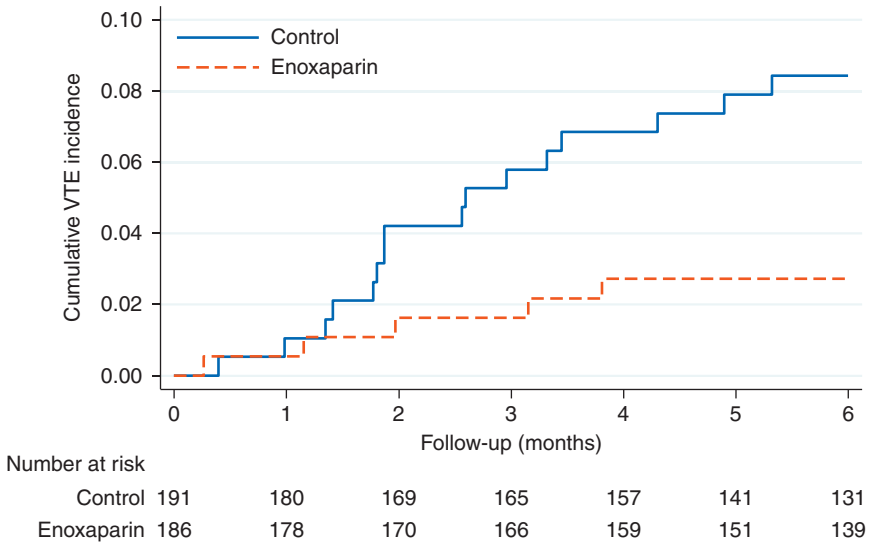

Figure 4. Cumulative incidence of first venous thromboembolism (VTE).

inhibition of, e.g., heparanase, vascular endothelial growth factor-A, fibroblast growth factors and platelet-derived growth factors [8, 10, 24]; however, the net effect of LMWH interactions within the complex tumor microenvironment is difficult to predict [29]. Specifically, a relatively low heparin concentration can stabilize protein ligands to potentiate their functional activity, whereas a higher concentration may compete with ligand interactions and down-stream functional effects on, e.g., angiogenesis and metastasis [24]. This argues for a relatively high dose of LMWH when repurposed as an anticancer agent, which was our rationale for investigating LMWH at an increased dose instead of the prophylactic dose used in previous studies. A potential drawback is the enhanced risk of bleeding complications; however, fatal bleedings occurred at a low incidence in both groups ($N = 3$ and 1, in the enoxaparin and control arm, respectively). A potential overestimation of total hemorrhages in the enoxaparin group may stem from a more vigilant registration of low grade events in the treatment arm.

We chose an open-label study design to spare control patients from placebo injections, and as the primary end point (OS) was not associated with observation bias. Although the actual administration of the study drug cannot be ascertained, good adherence is supported by the fact that VTE incidence was significantly lower in the enoxaparin than in the control arm, which had two cases of fatal pulmonary embolization. However, whether this difference was clinically relevant in terms of decreased morbidity and increased quality of life was not assessed in the present study. Notably, addition of prophylactic LMWH in the treatment of patients with pancreatic cancer with a particularly high incidence of VTE similarly showed a reduction in VTE incidence but no effect on OS [30].

During the 8 years that the study was open for enrollment, the treatment of SCLC remained unchanged. Thus, the treatment of the control group is still relevant. A recent trial [31] indicated that the addition of thoracic radiotherapy may improve outcome in SCLC patients with ED; however, this has not yet been implemented in clinical practice.

At present, the use of LMWH in cancer includes primary prophylaxis in patients at high risk of VTE, in patients diagnosed with VTE, and as secondary prophylaxis [32]. The present study provides strong support against a more general use of LMWH as a tumor-inhibiting agent and underlines the need for risk biomarkers to guide clinicians in tailoring individualized LMWH treatment [33].

Acknowledgements

We thank all the patients and their families, who participated in the trial, and all the investigators and staff who contributed their time and effort to make it a successful study.

Funding

This work was supported by the Swedish Research Councile (to MB, grant number: 2014-3421); the Swedish Cancer Society (to MB, grant number: 2014/378); the Skåne University Hospital donation funds (to MB, no grant number); the Medical Faculty, Lund University (to MB, no grant number); the Governmental funding of clinical research within the national health services (ALF) (to MB and EG, no grant number); the Gunnar Nilsson, Anna Lisa and Sven Eric Lundgren and Kamprad Foundations (to MB, no grant number); a restricted grant support from Sanofi Aventis, Sweden (to LE, no grant number); a donation by Viveca Jeppsson (to MB, no grant number); and received honoraria from Leo Pharma, AstraZeneca and Pfizer (to MB, no grant number).
The funders had no role in study design, data collection and analysis, decision to publish or preparation of the article.

Disclosure

The authors have declared no conflicts of interest.

References

1. Ervik M, Lam F, Ferlay J et al. Cancer Today: Cancer fact sheets: Lung Cancer, 05/2016 update; http://gco.iarc.fr/today.
2. Walters S, Maringe C, Coleman MP et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax 2013; 68(6): 551–564.
3. Blom JW, Doggen CJ, Osanto S et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005; 293(6): 715–722.
4. Rak J, Yu JL, Luyendyk J et al. Oncogenes, trousseau syndrome, and cancer-related changes in the coagulome of mice and humans. Cancer Res 2006; 66(22): 10643–10646.
5. Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. J Clin Oncol 2009; 27: 4834–4838.
6. Falanga A, Schieppati F, Russo D. Cancer tissue procoagulant mechanisms and the hypercoagulable state of patients with cancer. Semin Thromb Hemost 2015; 41(07): 756–764.
7. Petitou M, Casu B, Lindahl U. 1976-1983, a critical period in the history of heparin: the discovery of the antithrombin binding site. Biochimie 2003; 85: 83–89.
8. Niers TM, Klerk CP, DiNisio M et al. Mechanisms of heparin induced anti-cancer activity in experimental cancer models. Crit Rev Oncol Hematol 2007; 61(3): 195–207.
9. Bendas G, Borsig L. Cancer cell adhesion and metastasis: selectins, integrins, and the inhibitory potential of heparins. Int. J Cell Biol 2012; 2012: 676731.
10. Belting M. Glycosaminoglycans in cancer treatment. Thromb Res 2014; 133: S95–S101.
11. Noble S. Heparins and cancer survival: where do we stand? Thromb Res 2014; 133: S133–S138.
12. Gould MK, Dembitzer AD, Doyle RL et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130(10): 800–809.
13. Lee AY, Rickles FR, Julian JA et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol 2005; 23(10): 2123–2129.
14. Kakkar AK, Levine MN, Kadziola Z et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol 2004; 22(10): 1944–1948.
15. Klerk CP, Smorenburg SM, Otten HM et al. The effect of low molecular weight heparin on survival in patients with advanced malignancy. J Clin. Oncol 2005; 23: 2130–2135.
16. Altinbas M, Coskun HS, Er O et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. J Thromb Haemost 2004; 2(8): 1266–1271.
17. Lebeau B, Chastang C, Brechot JM et al. Subcutaneous heparin treatment increases survival in small cell lung cancer. "Petites Cellules" Group. Cancer 1994; 74(1): 38–45.
18. Akl EA, Gunukula S, Barba M et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database Syst Rev 2011; 19: CD006652.
19. Zhang J, Zhang YL, Ma KX et al. Efficacy and safety of adjunctive anticoagulation in patients with lung cancer without indication for anticoagulants: a systematic review and meta-analysis. Thorax 2013; 68(5): 442–450.
20. Macbeth F, Noble S, Evans J et al. Randomized phase III trial of standard therapy plus low molecular weight heparin in patients with lung cancer: FRAGMATIC Trial. J Clin Oncol 2016; 34(5): 488–494.

21. Stevenson JL, Choi SH, Varki A. Differential metastasis inhibition by clinically relevant levels of heparins–correlation with selectin inhibition, not antithrombotic activity. Clin Cancer Res 2005; 11(19 Pt 1): 7003–7011.
22. National Cancer Institute: Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 08/2006 update; https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (17 July 2015, date last accessed).
23. Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. Biometrics 2011; 67(1): 39–49.
24. Fuster MM, Esko JD. The sweet and sour of cancer: glycans as novel therapeutic targets. Nat Rev Cancer 2005; 5(7): 526–542.
25. Key NS, Khorana AA, Mackman N et al. Thrombosis in cancer: research priorities identified by a National Cancer Institute/National Heart, Lung, and Blood Institute Strategic Working Group. Cancer Res 2016; 76(13): 3671–3675.
26. Travis WD, Brambilla E, Nicholson AG et al. The 2015 World Health Organization Classification of Lung Tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10(9): 1243–1260.
27. Koizume S, Jin MS, Miyagi E et al. Activation of cancer cell migration and invasion by ectopic synthesis of coagulation factor VII. Cancer Res 2006; 66(19): 9453–9460.
28. Wojtukiewicz MZ, Hempel D, Sierko E et al. Protease-activated receptors (PARs)-biology and role in cancer invasion and metastasis. Cancer Metastasis Rev 2015; 34(4): 775–796.
29. Ori A, Wilkinson MC, Fernig DG. A systems biology approach for the investigation of the heparin/heparan sulfate interactome. J Biol Chem 2011; 286(22): 19892–19904.
30. Pelzer U, Opitz B, Deutschinoff G et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 Trial. J Clin Oncol 2015; 33(18): 2028–2034.
31. Slotman BJ, van Tinteren H, Praag JO et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015; 385(9962): 36–42.
32. Mandalà M, Falanga A, Roila F. ESMO Guidelines Working Group. Ann Oncol 2011; 22(Suppl 6): 85–92.
33. Angelini D, Khorana AA. Risk assessment scores for cancer-associated venous thromboembolic disease. Semin Thromb Hemost 2017; 43(05): 469–478.