Venous thromboembolism, coagulation and cancer
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CHAPTER

The effect of the low-molecular-weight heparin nadroparin on the survival in patients with cancer: A randomized trial

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In preparation
Chapter 7

ABSTRACT

Introduction
The low-molecular weight heparin, nadroparin, significantly prolonged the survival of cancer patients without venous thromboembolism in two studies. The present investigation was designed to confirm these findings.

Methods
A multicenter, randomized, open-label study was performed in patients with either non-small cell lung cancer (stage IIIB) within three months after diagnosis, hormone-refractory prostate cancer within six months after diagnosis or locally advanced pancreatic cancer within three months after diagnosis. Patients were randomized to nadroparin or no nadroparin next to their standard anti-cancer treatment. Subcutaneous nadroparin was given at therapeutic doses for two weeks followed by half therapeutic doses for four weeks. Patients were subsequently eligible for six cycles of two-week periods of nadroparin at therapeutic doses every six weeks. The minimum duration of follow up was 46 weeks. Outcomes were overall survival and major bleeding. All study outcomes were adjudicated by an independent and blinded committee.

Results
Between May 2006 and August 2008 a total of 503 patients were included. Of these 244 patients received nadroparin and 259 patients were allocated to no-nadroparin. The intention to treat population consisted of 197 patients with prostate cancer, 170 patients with non-small-cell lung cancer and 135 patients with pancreatic cancer. Full closure of the database is planned for the end of August 2009. At the preliminary analysis in July 2009 the overall mortality was 55.7% (n=136) in the nadroparin arm compared to 62.2% (n=161) in the no-treatment group (hazard ratio 0.92, 95% CI; 0.73-1.16). The median survival was 12.5 months in the nadroparin recipients and 11.9 months in the no-treatment subjects. Survival analyses in the three cancer types separately also did not show a statistically significant difference between the two groups, however, a trend for better survival in patients with prostate cancer was observed (hazard ratio 0.77, 95% CI; 0.52-1.15). The proportion of patients having at least one episode of major bleeding was comparable with 4.1% in the nadroparin recipients (n=10) and 3.5% in the no-treatment patients (n=9).

Conclusions
This study did not show a statistically significant nor clinically relevant benefit of nadroparin on overall survival. A trend for a better survival in prostate cancer patients receiving nadroparin was observed. The use of nadroparin was safe in terms of major and clinically relevant bleeding.
INTRODUCTION
Cancer may activate the coagulation system, which is known since Bouillaud described in 1823 three patients with cancer and venous thrombosis [1]. In addition, cancer cells utilize this system for their growth and metastases. The inhibitory effect of anticoagulants on cancer growth has been studied for the first time in a randomized controlled trial in 1994 in which small cell lung cancer patients without venous thromboembolism (VTE) were randomized to either unfractionated heparin (UFH) plus chemotherapy or chemotherapy alone. In a subgroup of patients with limited disease, UFH treatment was associated with a significant and clinically relevant survival benefit [2].

Subsequently, two meta-analyses evaluated the effect of low molecular weight heparin (LMWH) and UFH on survival in cancer patients treated for their venous thromboembolic disease. These drugs were given for 5-10 days as initial treatment followed in both groups by long term vitamin K antagonist treatment. The two meta-analyses revealed a survival benefit of LMWH over UFH with an odds ratio for total mortality of 0.72 (95% CI 0.55-0.96) at three months in the meta-analysis by Hettiarachchi and colleagues [3;4]. These analyses have several limitations. First, they concern studies with an other objective i.e. treatment of acute thrombotic disease and the follow up period was usually limited to 3 months. Second, only cancer patients with symptomatic VTE were included and therefore the relevance for cancer patients without VTE remains uncertain. Furthermore, two heparins were compared and therefore the benefit of LMWH alone is unclear. Finally, the types of malignancies varied widely. However, the effects were so impressive that randomized controlled trials of the effect of heparin on cancer growth in patients without VTE were subsequently initiated.

In two studies LMWH was added to a chemotherapy regimen in patients treated for small cell lung cancer and pancreatic cancer, respectively. Both studies concluded that LMWH improves the survival [5;6]. In the FAMOUS study a heterogeneous group of cancer patients were randomized to LMWH treatment or placebo for one year. In a post-hoc analysis cancer patients with a better prognosis appeared to benefit from LMWH treatment [7]. In the most recent study 302 cancer patients with advanced disease were given either 6 weeks of treatment with LMWH or placebo. Also in this study a significant survival benefit in cancer patients with a better prognosis at baseline was observed, i.e.15.4 months versus 9.4 months (hazard ratio 0.64, 95% CI; 0.45-0.90), although there also was a beneficial albeit smaller effect when all patients were considered [8]. This anti-cancer effect of LMWH was further supported by a post-hoc analysis of a randomized
trial of secondary VTE prevention in cancer patients comparing 6 months treatment with LMWH with vitamin K antagonists. In the subgroup of cancer patients with a prognosis of at least 6 months at study entry and treated with LMWH survival benefit was observed [9].

The results of these studies are intriguing. However, there are still some unresolved issues, which limit the evidence based clinical use. Most trials included a heterogeneous group of cancer patients and it is unclear whether the effect of heparin is comparable in many different cancer types. Furthermore, the applied regimens differed in dose, duration and type. The effect of a prophylactic dose of LMWH appeared to be less impressive than a therapeutic regimen. It is also debated whether repeat or prolonged administration of heparin may increase the effect.

We, therefore, designed a randomized study to assess the efficacy and safety of a LMWH, nadroparin, versus no treatment on survival in three different cancer types, i.e. patients with hormone-refractory prostate carcinoma, non-small-cell lung cancer stage IIIB or locally advanced pancreas carcinoma. These cancer types were selected since they have an expected comparable prognosis. The same nadroparin regimen was used as in our previous study, i.e. two weeks of therapeutic dose followed by four weeks prophylactic dose. Furthermore, patients randomized to nadroparin were encouraged to have an additional six subsequent cycles of a therapeutic dose of LMWH for two weeks followed by a four week wash-out period.

METHODS

Study population
Patients with histologically documented hormone-refractory prostate carcinoma within 6 months after diagnosis, with non-small-cell lung carcinoma (NSCLC) within 3 months after diagnosis, or with a locally advanced pancreas carcinoma within 3 months after diagnosis were eligible. Patients were excluded if, based on the clinical judgment of the treating physician, they had a life expectancy of less than three months at entry or a Karnofsky performance status of less than 60 points. Furthermore, they were not allowed to have an other indication for anticoagulant treatment, nor to be at high risk of bleeding. Also patients with severe thrombocytopenia (<50.000/mm3), renal insufficiency (creatinine clearance < 30ml/min), documented brain metastasis or pregnant women or women of child bearing potential who did not use effective means of contraceptive were
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not eligible. The study was approved by the respective institutional review boards of the participating centers. All included patients signed an informed consent. The study was supported by a grant from GlaxoSmithKline (Paris, France).

Treatment regimen
All patients received standard anti-cancer treatment according to local practice. Patients were randomized to nadroparin or no treatment; no placebo was given. Allocation of treatment proceeded centrally using an IVRS system. Patients were stratified for type of cancer and center. Patients allocated to nadroparin received therapeutic doses of once-daily subcutaneous nadroparin for two weeks, followed by half-therapeutic doses for an additional four weeks [8]. After these initial six weeks patients in the nadroparin arm were eligible for repeated cycles of nadroparin for a maximum of six cycles. These consisted of two week periods of therapeutic dose of nadroparin, always separated by a four week wash out period. The dose of nadroparin was body weight adjusted. Therapeutic doses were 7600 IU per day for patients with a body weight less than 50 kilograms, 11400 IU per day for patients between 50 and 70 kilograms and 15200 IU o.d. for those above 70 kilograms. For the 4 week half-therapeutic dose period pre-filled syringes were provided containing 3800 IU for patients less than 50 kilograms, 5700 IU for patients with a body weight between 50 and 70 kilograms and 7600 IU for patients above 70 kilograms. Patients or family members were instructed how to inject the study treatment, but home care or equivalent nursing services were arranged when indicated. In the event of severe thrombocytopenia (<50,000/mm3), treatment was interrupted.

Follow up
The total duration of study medication was 46 weeks, including the wash-out periods, which was also the minimum duration of follow up. Visits were scheduled at weeks 6 and 10, thereafter patients were contacted at 6 week intervals. During the visits special attention was paid to bleeding and venous and arterial thrombotic events. A standardized questionnaire was used to obtain information about outcomes and anti-neoplastic therapy. If necessary, the treating physician, the family doctor, or the patient’s chart were consulted to complete information.
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Outcome measures
The primary efficacy outcome was all cause mortality. Safety outcomes were major and clinically relevant non-major bleeding during the study medication period. Major bleeding was defined as overt bleeding which was associated with a decrease in hemoglobin of more than 2g/dL, or which lead to transfusion of two or more units of blood. Furthermore, retroperitoneal, pericardial, intracranial bleeding or bleeding located in a critical organ, or leading to death were classified as major bleeding. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding using definitions as described earlier [10].

Statistical analysis
It was calculated that approximately 250 patients per arm, i.e. a total of 500 patients, needed to be included. With an expected minimal relative risk reduction of 20% in the nadroparin group compared to the no-treatment group and a death rate of 70% among the no-treatment patients during the follow-up period, this number of patients will give a power of 85% (type II error=15%) at an overall significance level of 0.05 (two-sided type I error=5%). Even if the observed mortality in the no-treatment group is as low as 50%, there would be still enough power (90%) to detect an overall 30% risk reduction. With an expected risk reduction of 30% in the nadroparin group compared to the no-nadroparin group, and a death rate of 70% among the included patients during the follow up period, and an inclusion of 84 patients per cancer type per treatment arm there will be a power of 75% at a significance level of 0.05 (two sided type I error=5%) to detect a difference in one or more of the cancer subgroups.

Cox-regression models were employed and hazard ratios were calculated for survival and were adjusted for cancer type. Ninety-five percent confidence intervals were calculated when appropriate. For stratifying variables and potential confounders all analyses were corrected. The primary efficacy analysis was based on an intention-to-treat principle. A statistical analysis plan was agreed prior to database closure by the steering committee. The data were extracted by biostatisticians of GlaxoSmithKline and verified by the steering and writing committee.
RESULTS

A total number of 503 patients were included between May 2006 and August 2008. Seventy-three centers participated, which were located in 10 countries. Two hundred and forty-four patients were randomized to nadroparin next to standard anti-cancer therapy, whereas 259 patients were allocated to the no-nadroparin group (Table 1). The mean age was similar in both groups with 65 years. Of the nadroparin recipients 197 (81%) were men compared to 206 (80%) in the no-nadroparin arm. Of the intention to treat population in the nadroparin arm 41% (n=100) had prostate cancer, 33% (n=81) had non-small cell lung cancer and 26% (n=63) suffered from hormone refractory prostate cancer. In the no-treatment arm the distribution was 38% (n=97), 34% (n=88) and 28% (n=72), respectively. In this group two patients who were initially diagnosed to have lung cancer proved to have lymphoma after extensive revision. They are included in the intention to treat analysis.

Table 1 - Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nadroparin (n=244)</th>
<th>No Nadroparin (n=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>65 (10)</td>
<td>65 (9.8)</td>
</tr>
<tr>
<td>Men</td>
<td>81% (n=197)</td>
<td>80% (n=206)</td>
</tr>
<tr>
<td>Prostate</td>
<td>41% (n=100)</td>
<td>38% (n=97)</td>
</tr>
<tr>
<td>Lung</td>
<td>33% (n=81)</td>
<td>34% (n=88)*</td>
</tr>
<tr>
<td>Pancreas</td>
<td>26% (n=63)</td>
<td>28% (n=72)</td>
</tr>
</tbody>
</table>

* Two lung cancer patients proved to have a lymphoma after revision of the pathology.

At the preliminary analysis in July 2009 the overall mortality was 55.7% (n=136) in the nadroparin arm compared to 62.2% (n=161) in the no-treatment group (adjusted hazard ratio 0.92, 95% CI; 0.73-1.16). The median survival was 12.5 months in the nadroparin recipients and 11.9 months in the no-treatment subjects (Table 2). No difference in the survival curves was observed (data not shown).

Table 2 - Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median survival in Months [IQR]</th>
<th>Adjusted hazard ratio*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadroparin</td>
<td>12.5 [10.7-15.4]</td>
<td>0.92 [0.73-1.16]</td>
<td>0.48</td>
</tr>
<tr>
<td>No nadroparin</td>
<td>11.9 [10.2-13.7]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for cancer type.
Of all patients with a hormone refractory prostate carcinoma 43.0% \((n=43)\) died in the nadroparin arm compared to 56.7% \((n=55)\) in the no-nadroparin group (Table 3). Regarding the non-small cell cancer patients treated with nadroparin 56.8% \((n=46)\) died compared to 59.1% \((n=52)\) in the no-treatment group. Finally, 74.6% \((n=47)\) of the pancreatic cancer patients in the nadroparin group died, whereas 73.6% \((n=53)\) of the patients with pancreatic cancer in the no-nadroparin arm died (Table 3).

In 10 patients \((4.1\%)\) treated with nadroparin a major bleeding occurred compared to 9 patients \((3.5\%)\) in the no-treatment group. Also the number of patients who had at least one major or clinically relevant bleeding was comparable with 22 patients \((9.0\%)\) in the nadroparin group and 21 of the no nadroparin patients \((8.1\%)\).

Table 3 - Number of deaths per cancer type

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Nadroparin</th>
<th>No-nadroparin</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (197)</td>
<td>43/100 (43.0%)</td>
<td>55/97 (56.7%)</td>
<td>0.77 (0.52-1.15)</td>
</tr>
<tr>
<td>Lung (170)</td>
<td>46/81 (56.8%)</td>
<td>52/88 (59.1%)</td>
<td>0.92 (0.62-1.37)</td>
</tr>
<tr>
<td>Pancreas (135)</td>
<td>47/63 (74.6%)</td>
<td>53/72 (73.6%)</td>
<td>1.10 (0.73-1.63)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This preliminary analysis of a large randomized controlled study on the effect of nadroparin, a LMWH, on the survival of patients with advanced cancer without an other indication for anticoagulation showed no overall survival benefit for those treated with nadroparin. A median survival of 12.5 months was observed in the nadroparin recipients compared to 11.9 months in the no-treatment arm (hazard ratio 0.92, 95% CI; 0.73-1.16). A comparable number of bleeding episodes was observed in both groups with 4.1% in the nadroparin recipients and 3.5% in the no-treatment patients.

Our hypothesis based on at least two earlier trials in cancer patients was that nadroparin treatment would lead to a risk reduction of approximately 30%, however, much to our surprise there was no significant nor clinically relevant difference in all cause mortality.

In the design of the study we took care of the following aspects. Firstly, the type of cancer was limited to three groups with a projected comparable median survival of approximately 10 months in the no-treatment arm and we observed a median survival of 11.9 months in those patients not receiving LMWH, which varied from 10.4 to 15.0 in
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the three groups. Hence, this objective was met and therefore the absence of an effect of LMWH is unlikely due to the selection of cancer types. The second aspect is the applied treatment regimen. The same regimen as in the successful MALT study was used initially consisting of two weeks of a therapeutic dose followed by half that dose for four weeks. Moreover, patients were encouraged to receive a maximum of six repeated cycles of nadroparin in a therapeutic dose for two weeks with a four weeks wash out period in between. This latter was based on the hypothesis that repetitive exposure of LMWH may increase the effect, as well as trying to circumvent adaptive processes in the cancer cells when LMWH would be administered continuously for a prolonged period of time. It is unlikely but not impossible that the repeated gifts may have diminished the anti-cancer effect. Thirdly, the primary sample size considerations were based on conservative assumptions. With an expected death rate of 70% in the non-treated patients the study had a 85% power to detect a minimum relative risk reduction in total mortality of 20%. Even with a 50% death rate in the no treatment group our study had a power of 90% to detect an overall 30% risk reduction. In the present study the all cause mortality was 62.2% in the no treatment group. However, a non significant risk reduction of 8% was observed with a lower boundary of the 95% confidence interval of 27%. It should be noted that in the prostate subgroup there was a reduction in total mortality of 23%. This may indicate a differential effect of LMWH in the prostate group relative to the two other cancer groups.

At this point, no information on the study discipline and on the number of patients lost to follow up is available yet. Future analyses are planned to assess the influence of nadroparin treatment on cancer progression, and the subgroup of patients with a better prognosis. Furthermore, the analyses will be adjusted for the number of patients in the no treatment group who received a course of low molecular weight heparin during the study period and for the effects of the applied cancer therapies.

Bases on this premature analyses we conclude that this study did not show a statistically significant or clinical relevant beneficial effect on the overall survival in cancer patients treated with nadroparin. Given the other ongoing studies in this area, as well as the previous data, we have to await whether our findings are the correct answer or whether this was a play of chance.
REFERENCE LIST


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