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DOES LOW MOLECULAR WEIGHT HEPARIN IMPROVE THE SURVIVAL OF CANCER PATIENTS? AN INTERIM SAFETY REPORT OF A RANDOMIZED DOUBLE BLIND PLACEBO-CONTROLLED STUDY

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SUMMARY

BACKGROUND
Recent randomized trials have indicated that low molecular weight heparin (LMWH), as compared to unfractionated heparin (UFH), improves survival of patients with cancer. Therefore, a study was designed to test whether LMWH administration prolongs survival of patients with documented malignancy. In this randomized, placebo-controlled trial, patients with non-curable cancer and a limited life expectancy receive either LMWH or matching placebo for a period of 6 weeks. Because it is known that the risk of bleeding in cancer patients treated with antithrombotics is higher, the objective of this interim report is the evaluation of safety of LMWH treatment in this cancer patient population.

METHODS
A total of 151 patients with non-curable solid malignant tumors have so far been randomized. The total number of patients to be included is 300. The minimal duration of follow up is 6 months. During the first 2 weeks, patients randomized to the LMWH group receive a therapeutic weight adjusted dose (<50 kg: 3800 IU anti-Xa; 50-70 kg: 5700 IU anti-Xa; >70 kg: 7600 IU anti-Xa), twice a day subcutaneously (s.c). This dose is subsequently halved for the next 4 weeks. Patients allocated to the placebo group are treated with identical appearing injections in a similar fashion.

RESULTS
So far, the study patients include 66 men and 85 women with a mean age of 62 years. The types of malignancies vary widely. Of the 151 patients, 128 (85%) have completed the 6-weeks treatment period. Twenty-three patients stopped treatment prematurely for various reasons. Among others, 3 patients stopped because of major bleedings and 4 patients because of minor bleedings. A total of 101 patients have completed 6 months of follow up. Fourty-two patients (42%) died within 6 months of randomization. No patient was lost to follow up. The 3 patients with major bleeding belonged to the same treatment group. Assuming that this group was the LMWH-group and that half of the patients received LMWH, the incidence of major bleeding is 4.0% (95% CI: 0.83-11.25%).

INTERPRETATION
The risk of major bleeding during the initial course of anticoagulant therapy is approximately 1-2%. Since all patients in this study have cancer, a higher incidence of bleeding complications is expected. Therefore, the observed incidence of major bleeding appears acceptable. Since the study has remained blinded, no conclusions can be drawn on the effects of LMWH on mortality. However, the 6-months mortality rate of all 101 patients of 42% corresponds with the expected total mortality. Therefore, it can be concluded that the target population is included in this study and that the power of the study is sufficient to detect mortality reduction due to treatment, if any.
INTRODUCTION
Cancer patients are known to have an increased risk for venous thromboembolic complications (1). Consequently, a significant proportion of cancer patients receive anticoagulants as treatment or as prophylaxis of venous thrombosis. For many years, intravenous unfractionated heparin (UFH) has been the drug of choice for the initial treatment of venous thromboembolism (VTE). Recent comparative trials have shown that low molecular weight heparins (LMWH) are at least as safe and effective as UFH in the treatment of VTE (2). Interestingly, results of a pooled analysis of these trials also indicated that LMWH may improve survival of patients with cancer (3). Patients with cancer who received LMWH for their VTE had 40% reduction in 3-month mortality as compared to cancer patients who were treated with UFH. In contrast, mortality rates of VTE patients who had no cancer were similar in both groups. These results indicate that LMWH, but not UFH, have a direct inhibitory effect on tumor progression. Other possible explanations are less likely, because incidences of thrombotic and bleeding complications were comparable in both treatment groups and adjustment for major prognostic factors did not alter the observed differences in mortality. Furthermore, there is no reason to suggest increased mortality in the UFH group, since clinical studies comparing UFH to placebo or no treatment in cancer patients did not reveal an increased risk (4), whereas a number of experimental studies demonstrated inhibitory effects of UFH on cancer metastasis in rats and mice (5;6).
A beneficial effect of LMWH on survival of cancer patients has to outweigh the risk of bleeding complications during treatment. The risk of major bleeding in patients with VTE who are treated with therapeutic doses of LMWH for one week is estimated to be 1-2% (7), but the risk in patients that also have cancer is known to be higher (8).
The MALT study (malignancy treatment with LMWH) was designed to test the hypothesis that LMWH administration improves survival of patients with documented malignancy. In this randomized, placebo-controlled trial, patients with non-curable cancer and a limited life expectancy receive either LMWH or matching placebo for a period of 6 weeks, with a follow up of 6 months. The objective of this interim report is to evaluate safety of LMWH treatment in the patient population included in the MALT study. Baseline characteristics of the thus far included patients are described and the incidence of adverse events is descriptively presented for the entire patient group, since the study has remained blinded.

METHODS
PATIENTS AND STUDY DESIGN
The MALT study is a randomized, double blind, placebo-controlled clinical trial to assess effects of LMWH treatment on survival of non-curable patients with solid malignant tumors. Patients in 8 participating hospitals in the Netherlands and Italy are randomized to either LMWH or placebo treatment for a period of 6 weeks. The minimal duration of follow-up is 6 months. Inclusion and
exclusion criteria for patients are presented in Table 1. The study protocol has been approved by the institutional review board of each hospital and informed consent is obtained from each participating patient.

**INTERVENTION**

During the first 14 days, patients randomized to the LMWH-treatment group receive a therapeutic weight-adjusted dose of nadroparin (Fraxiparine®; Sanofi-Winthrop, France) (<50 kg: 3800 IU anti-Xa; 50-70 kg: 5700 IU anti-Xa; >70 kg: 7600 IU anti-Xa), s.c. twice a day. After the first 2 weeks of treatment, the dose is halved and a single daily s.c. injection is given for the next 4 weeks. The rationale of this treatment scheme is to provide a maximum exposure to nadroparin, with a minimal risk of hemorrhage. Patients allocated to the placebo group are treated with identical appearing injections in a similar fashion as for the LMWH-treatment.

**Exclusion:**
- Age less than 18 years
- Pregnancy
- Other indications for anticoagulant treatment
- Contra-indications for low molecular weight heparin
- Radiotherapy or chemotherapy leading to thrombocytopenia (<50x10^4 ml) during the first 2 weeks of treatment
- Slow progression of malignancy with expected survival of more than 18 months

**Inclusion:**
- Presence of solid non-curative malignancy
- Written informed consent

*Table 1. Inclusion and exclusion criteria for patients in the Malt study*

**SAMPLE SIZE CONSIDERATIONS**

On the basis of the expected mortality rate of 40-45% after a follow up period of 6 months in the placebo group and a risk reduction of 30%-40% in the LMWH-treatment group with an alpha-error of 0.05 and a beta-error of 0.2, it was calculated that a total of 150 patients has to be included in each group.

**FOLLOW UP**

The first follow up visit is scheduled 7 to 14 days after randomization, whereas the second visit is between days 28 to 42. Clinical status and progression of disease are recorded during each of these visits. Survival at month 6 is determined. When necessary, the responsible family physician or oncology clinic is contacted.
OUTCOME MEASURES

The primary outcome measure of the study is total mortality in the two groups after 6 months of follow up. Causes of death are recorded on the basis of information available from notes made by physicians, hospital records, autopsy reports and other appropriate sources of information. The primary safety outcome measure is the incidence of clinically apparent major hemorrhages during the 6 weeks (plus 24 h) of anticoagulant treatment.

HEMORRHAGE

A hemorrhage is considered as major when it is clinically overt and associated with a fall in hemoglobin level of 2 mmol/L or more, when it leads to a transfusion of two or more units of packed red cells, when it is a symptomatic retroperitoneal or intracranial bleeding, or when the bleeding warrants permanent cessation of treatment. Minor bleeding is defined as clinically unusual overt bleeding, which does not meet the criteria for major bleeding.

ANALYSIS

In this interim safety report, the incidence of adverse events is presented descriptively for the whole group. The incidence of major bleedings is presented separately for each group, but the study remained blinded. Therefore, it is not possible to determine whether patients with major bleeding received LMWH or placebo-treatment.

RESULTS

At the time of this interim safety analysis (May 2000), 151 cancer patients, 66 men and 85 women, have been randomized to receive double blind treatment. The mean age of the patients that are included is 62 years (SD 10). The prevalence of malignancies according to their primary site is presented in Table 2.

Of the 151 randomized patients, 128 (85%) completed the 6-weeks treatment period. Twenty-three patients stopped treatment prematurely because of the following reasons:
- 5 patients because of death due to progression of malignancy
- 3 patients because of non-fatal major bleedings
- 4 patients because of minor bleedings
- 2 patients because of thromboembolic complications
- 2 patients because of allergic skin reactions
- 1 patient because of surgery
- 6 patients because of withdrawal of informed consent.

A total of 101 patients have completed 6 months of follow up. No patient has been lost to follow up. Fourty-two patients (42%) died within 6 months of randomization.
<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>38</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>16</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>28</td>
</tr>
<tr>
<td>Gastric/esophageal cancer</td>
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<td>Pancreatic cancer</td>
<td>8</td>
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<tr>
<td>Renal cancer</td>
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</tr>
<tr>
<td>Prostate cancer</td>
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<td>Cervical cancer</td>
<td>11</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3</td>
</tr>
<tr>
<td>Metastasis, primary tumor unknown</td>
<td>6</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>151</strong></td>
</tr>
</tbody>
</table>

Table 2. Type of malignancies of patients included in the Malt study.

**Bleeding complications**

There were 3 major and 4 minor bleeding complications in the study population of 151 cancer patients that were included in the Malt study. Among the 3 major bleedings, one patient with metastasized bladder carcinoma developed hematemesis at the 9th day of treatment, requiring hospitalization and blood transfusion. The second patient had small cell lung cancer with bone metastases and complained of squinting at the 6th day of treatment. A CT scan revealed multiple, previously unknown intracerebral metastases, one of those showing hemorrhage. The third patient had pancreatic cancer and developed melena at the 4th day of treatment, requiring hospitalization and blood transfusion.

The 4 minor bleedings consisted of single episodes of hematemesis and skin hematomas. A patient with metastasized lung cancer developed a single episode of hematemesis at the 13th day of treatment. Gastroscopy showed metastases in the esophagus, which was confirmed by pathological diagnosis of biopsies. The second patient with metastasized renal cancer and pre-existing severe renal insufficiency developed skin hematomas on the thorax and limbs after 3 weeks of medication, without significant changes of hemoglobin. The third patient with lung cancer developed skin hematomas on the thorax on the 4th day of treatment. This patient received acetyl salicylic acid and prednisolon in addition to study medication. The fourth patient developed a large hematoma on the right leg on the 11th day of study medication, without significant changes of hemoglobin.

The 3 patients with major bleeding belonged to the same treatment group. Assuming that this group was the LMWH group and that half of the patients (75) received LMWH, the incidence of major bleeding was 4.0% (95% CI: 0.83-11.25%).
OTHER ADVERSE EVENTS

Five patients died during treatment with study medication due to progression of malignancy. One patient was diagnosed with pulmonary embolism on the 3rd day of treatment and one patient with deep vein thrombosis on the 12th day of treatment. In both patients, study medication was stopped and the patients were treated with LMWH and vitamin K antagonists. Two other patients developed allergic skin reactions, which were considered to be related to study medication. Study medication was stopped in one patient because of surgery that was required because of progression of malignancy.

DISCUSSION

Before the use of LMWH can be considered for anti-cancer therapy, prolonging effects of LMWH on survival of cancer patients should outweigh risks of bleeding complications during treatment. Therefore, the major aim of this interim analysis was determination of safety of a 6 week course of LMWH treatment in patients with cancer. It should be realized that LMWH recipients received a therapeutic dose during the first 14 days, whereas for the following 4 weeks, half of this dose was given. The results show that approx. 85% of the included patients completed the initial 6-week treatment period without complications. Among 151 cancer patients who received study medication, 7 patients stopped prematurely because of bleeding complications, mainly occurring in the first 14 days of the study. These included 3 major hemorrhages. Since all patients with major bleeding belonged to the same treatment group, and assuming that half of the patients included received LMWH, the incidence of major bleeding in this study is 4.0%. This incidence is considered clinically acceptable but higher than the incidence of major bleeding in patients treated with LMWH for VTE in randomized trials, in which safety of LMWH treatment was investigated. In a pooled analysis of randomized studies that compared efficacy and safety of LMWH with that of UFH for the treatment of VTE, the overall risk of major bleeding in patients treated with LMWH, in therapeutic dosages, was 1-2% (7). However, it has been shown that cancer-patients are at increased risk to develop hemorrhages when they receive anticoagulants as compared to patients without malignancy (8). Since all patients randomized in the MALT study are cancer patients with poor prognosis (with life expectancy of less than 18 months), a higher incidence of bleeding complications is expected. Therefore, the observed incidence of major and minor bleeding complications appears to be within the expected range for LMWH therapy. It is obvious that the potential benefit of LMWH therapy on survival, if present, needs to be balanced against this risk of bleeding complications.

Since the study remained blinded during this safety analysis, no conclusions can be drawn about the effects of LMWH on mortality of cancer patients. However, the results show that the total mortality rate observed among the 101 patients of both treatment groups who completed 6 months of follow...
up (42%) corresponds with the expected total mortality. Therefore, it is reasonable to conclude that the target population is included in this study and that the power of the study is sufficient to detect the expected mortality reduction.

ACKNOWLEDGEMENT
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REFERENCES