Name of Sponsor/Company: University Hospital Essen, Germany	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use only)
Name of Finished Product: Clexane®		
Name of Active Ingredient: Enoxaparin sodium		

Title of Study:
„Prospective, randomised, controlled, open single-centre trial on thromboembolic prophylaxis with Enoxaparin in non-surgical cancer patients under systemic antineoplastic therapy“

(Note: Title in ISRCTN: „Thromboembolic prophylaxis with enoxaparin in non-surgical cancer patients under systemic antineoplastic therapy“)

Study Acronym:
VTETumor02

EudraCT No.:
2007-002036-28

ISRCTN No.:
ISRCTN25616445 (➔ https://doi.org/10.1186/ISRCTN25616445)

Investigators:
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Study centre(s):
Department of Medical Oncology of the West German Cancer Center together with Clinic and Policlinic for Angiology at the University Hospital Essen, Germany

Publication (reference):
N. A.

Studied period (years): 1,86 **Date of first enrolment:** August 11, 2008 **Date of last completed:** June 21, 2010	**Phase of development:** Phase II pilot study

Objectives:

In a registry survey at the University Hospital Essen, 6 risk factors (inpatient treatment, chemotherapy, history of thrombosis, family history of thrombosis, elevated CRP and fever) for the risk of thrombosis in tumor patients were described.
All patients included in this study were hospitalized on systemic antineoplastic therapy at baseline, thus already having 2 risk factors. The present study was designed to answer the question of whether the risk of thrombosis can be reduced by prophylactic administration of low-molecular-weight heparin (enoxaparin 40 mg) in hospitalized tumor patients in whom another 1-3 risk factors are present.

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Enoxaparin 40 mg is approved in Germany for prophylaxis in nonsurgical patients, but there is no specific approval for longer-term (>2 weeks) administration in nonsurgical oncologic patients. Therefore, this was a phase II pilot project.
In the present study, we recorded at baseline whether and which of the risk factors described in the registry survey were present.
Patients were then randomized to receive either enoxaparin 40 mg s.c. daily for 24 weeks or no treatment. The main objective of the study was to compare the treated and untreated groups with respect to the occurrence of a venous thromboembolic event (VTE). All patients were followed-up for 24 weeks or until the occurrence of a VTE. Furthermore, the tolerability of the therapy was recorded.

Methodology:

- unicenter, randomized, controlled trial
- open parallel group design with one null arm
- Study treatment: after randomization, either enoxaparin 40 mg s.c. daily for 24 weeks (treatment arm) or no treatment (null arm)
- Method of assignment to treatment arm: central 1:1 randomization.
- Sequence and duration of all study arms: The study duration was 24 weeks in total. There was a baseline examination, which included sonographic examination for VTE. In addition, platelet checks were performed in the treatment arm before the first enoxaparin injection one day after the first injection and thereafter at 3-day intervals for 3 weeks after the first enoxaparin injection. In both arms, patients were followed up every 3 to 4 weeks to assess current tumor therapy, survival status, safety parameters, and the occurrence of VTE. At the end of the study, a final examination including a further sonographic examination was performed.
- Interim evaluations did not take place.

Number of patients (planned and analysed):

Case number: the planned case number was 160 patients. A total of 30 patients were included in the study until discontinuation.

Diagnosis and main criteria for inclusion:

- Male and female patients aged ≥ 18 years.
- Inpatient treatment at study inclusion
- Patient is also able to continue heparin prophylaxis independently on an outpatient basis
- 1 to 3 of the following 4 risk factors are present:
    - History of thrombosis,
    - family history of thrombosis,
    - fever within 4 weeks before study entry,
    - elevated CRP levels within 4 weeks before study entry
- Proficient in the German language
- Diagnosis of malignant disease
- Under systemic antineoplastic therapy
- Expected life expectancy > 24 weeks
- Patient willing and able to come regularly for examination and follow-up appointments

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Exclusion criteria:

- Women of childbearing age who do not have adequate protection against conception and use a double barrier (intrauterine device plus condom or spermicide plus condom) or women who are not postmenopausal (there should be more than 12 months of amenorrhea).
- Contraceptives
- Pregnancy or lactation (For patients of childbearing age, pregnancy must be ruled out by means of a pregnancy test or other suitable methods. A note to this effect must be included in the medical record).
- Renal cell carcinoma, meningioma
- Therapy with neoangiogenesis inhibitors (e.g. bevacizumab, sorafenib, sunitinib)
- Alcoholics, medication or drug addicts
- Venous thromboembolic event (VTE) within the last 24 weeks
- Low body weight (women < 45 kg, men < 57 kg)
- Known intolerance/hypersensitivity to enoxaparin, heparin, or heparin derivatives, including other low molecular weight heparins
- Clinically relevant coagulation disorder (patients are asked whether they or their family members have one of the most common thrombophilic coagulation disorders in Germany (APC resistance, protein C or S deficiency, ATIII deficiency, prothombic combination, phospholipid antibody syndrome). If the question is answered in the affirmative for self, these patients will not be included. If the question is answered in the affirmative for the family, a laboratory check will be performed to determine whether this coagulation disorder is also present in the patient).
- Complete immobility
- Simultaneous presence of all 4 of the following risk factors: thrombosis in the anamnesis, thrombosis in the family, fever within 4 weeks before study entry, elevated CRP values within 4 weeks before study entry.
- Current HIT II or HIT II known from medical history.
- Platelet count < 50,000 /µl
- Known severe renal insufficiency (GFR ≤ 30 ml/min)
- Surgery within the last 6 weeks or during the study period
- Injuries within the last 6 weeks
- Recent clinically relevant bleeding (within the last 4 weeks)
- Suspicion of hemorrhagic stroke or other intracranial hemorrhage
- Hemorrhagic stroke or other intracranial hemorrhage within the past 6 months
- Acute or history of known intracranial disease (e.g., brain tumor, aneurysma)
- History of gastric or intestinal ulcers
- History of severe liver or pancreatic dysfunction
- Uncontrollable severe hypertension
- Abortus imminens
- Suspected vascular retinopathy, vitreous hemorrhage, or other intraocular hemorrhage
- Acute internal disease requiring thromboprophylaxis (e.g. pneumonia, myocardial infarction, sepsis, inflammatory bowel disease, NYHA III and IV heart failure, respiratory disease not requiring ventilation, rheumatic disease).
- acute neurological disease
- endocarditis
- participation in a clinical study within the last 4 weeks
- participation in this study at an earlier time
- concurrent participation in another clinical trial

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Test product, dose and mode of administration, batch number:

The dosage of enoxaparin was 40 mg daily s.c. for 24 weeks for patients in the treatment arm. Patients in the null arm received no treatment.

Duration of treatment:

24 weeks

Reference therapy, dose and mode of administration, batch number:

N.A.

Criteria for evaluation:

Efficacy:

The occurrence of venous thromboembolic events (VTE; pulmonary embolism or thrombosis, symptomatic or asymptomatic) was first detected by questioning the patient, who was informed at the beginning of the study how to recognize the symptoms of a thrombosis / pulmonary embolism. If VTE was suspected, sonography was performed as compression sonography of the common femoral vein, superficial femoral vein, popliteal vein, posterior tibial veins, fibular veins, jugular veins, and subclavian veins on both sides to check for venous thromboembolic events (VTE).
If thrombosis was detected, pulmonary embolism was confirmed or ruled out by CT scan.
If there were clinical signs of pulmonary embolism, the patient received a CT scan directly. If pulmonary embolism was detected, compression ultrasonography of the peripheral veins was followed. Imaging procedures to detect VTE were performed by the angiology department.
Testing of Glomerular Filtration Rate (GFR) served as measure of kidney function. GFR rates below 30 during the study led to an exclusion of the affected patients.

Safety:

Laboratory parameters (platelet count, CBC, D-dimers, coagulation factors (AT III, aPTT, INR, fibrinogen), CRP, creatinine) and the question of the occurrence of clinically relevant bleeding were used to determine tolerability/safety. Adverse events (AE) and/or adverse reactions were continuously registered during the trial. Regular blood count checks have been part of oncological patient management in tumor patients undergoing chemotherapy. Additional blood counts for the detection of HIT II have were not indicated. If the platelet count falled below 50,000, a test should be performed to determine if the thrombocytopenia was heparin-induced. If so, this was reported to the sponsor as a serious adverse event (SAE). Similarly, the occurrence of clinically relevant bleedings was reported as a SAE to the sponsor.

Statistical methods:

Primary endpoint was the occurrence of pulmonary embolism or thrombosis (symp-tomatic or asymptomatic). The characteristic was evaluated dichotomously.
Since the study was terminated, the evaluation was only descriptive. Dichotomous data were analyzed with Fisher's exact test, continuous data with the U-test.

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Secondary endpoints analyzed:

- Safety – Laboratory testings
- Occurrence of HIT II (= Heaprin induced thrombocytopenia type II)
- Incidence of clinically relevant bleeding
- All-cause mortality
- Evaluation of the risk assessment for VTE described in the Annals of Oncology 2006.

Subgroup analyses were made for sex, patient age, and relevant risk factors of interest.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

There were 4 VTE in patients in the null arm and 1 in patients in the treatment arm
Patient compliance was 79%. Patients who did not inject themselves once or participated in the study for less than 15 days were excluded from the calculation of compliance.
All patients who received heparin prophylaxis were found to tolerate this prophylaxis well.
A reduced efficacy of tumor therapy due to the administration of enoxaparin could not be determined. The efficacy of tumor therapy was almost the same in both treatment arms.

SAFETY RESULTS:

Five deaths, 20 other serious adverse events (SAE), and 44 other adverse events (AE) occurred within the study. With three exceptions, no association between treatment with enoxaparin and the occurrence of each AE could be established. For two SAEs (bronchopulmonary infection, thrombocytopenia), the association between enoxaparin administration and the occurrence of the event was rated as "unlikely." For one SAE (hyperkalemia), the association between enoxaparin treatment and the occurrence of the event was rated as "possible."
For three SAEs (diverticulitis, exsiccosis, thrombocytopenia), treatment with enoxaparin was temporarily interrupted during or after the adverse event.

CONCLUSION:

A statement on efficacy cannot be made, since only 30 patients were included in the study and, in addition, there were many study discontinuations, particularly in the treatment arm.
The more frequent observation of pancytopenias in the treatment arm compared to the null arm cannot be clearly attributed to the treatment with enoxaparin in view of the small number of patients and the simultaneously administered myelosuppressive chemotherapy.

Date of the report:

September 20, 2022

CONSORT Flow Diagram VTETumor02