Phase I study of dalteparin, a low molecular weight heparin (LMWH), in combination with Sunitinib (SU11248), an oral, selective multitargeted tyrosine kinase inhibitor, as first line treatment, in patients with metastatic renal cell carcinoma

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON39888

Source
ToetsingOnline

Brief title
Dalteparin plus Sunitinib in patients with renal cell cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney cancer, renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Pfizer,Roswell Park Cancer Institute (Buffalo)

Intervention

Keyword: Dalteparin, Renal cell cancer, Sunitinib

Outcome measures

Primary outcome

1. Objectives

1.1 Objectives phase I study

1 To determine the recommended dosing for the combination of Sunitinib and

Dalteparin in patients with metastatic renal cell carcinoma.

2 To evaluate safety and tolerability for the combination of Sunitinib and

Dalteparin in patients with metastatic renal cell carcinoma.

3 To determine early signs of clinical activity of the combination of Sunitinib

and Dalteparin in patients with metastatic renal cell carcinoma.

Secondary outcome

1.3 Secondary Objectives:

1 To determine the clinical response rate of Sunitinib and Dalteparin in

patients with metastatic renal cell carcinoma.

2 To determine time-to-progression (TTP) and overall survival amongst patients

with metastatic renal cell carcinoma receiving Sunitinib and Dalteparin.

3 To determine the effect of Sunitinib alone and Dalteparin alone compared to

the combination of Dalteparin plus Sunitinib on plasma coagulation parameters.

4 To determine the effect of Sunitinib alone and Dalteparin alone compared to

the combination of Dalteparin plus Sunitinib on angiogenesis parameters in

blood.

Study description

Background summary

See details in protocol
Based on preclinical and clinical data on the concomitant activation of the coagulation and angiogenesis cascade in cancer patients, we hypothesize that the combination of anticoagulants, in particular LMWHs, plus Sunitinib can be safely administered. Sunitinib is an accepted first line treatment for metatastic renal cell carcinoma patients. The proposed study is designed to test these hypotheses in a phase I feasibility trial in patients with renal cell cancer in which Sunitinib has shown antitumor activity.

Study objective

The proposed study is designed to test the hypothesis that the combination of anticoagulants, in particular Dalteparin plus Sunitinib, can be safely administered in a phase I feasibility trial in patients with renal cell cancer in which Sunitinib has shown antitumor activity as described above.

Study design

Phase I design
The starting dose of Dalteparin will be 70 IU/kg/day (= prophylactic dose for thrombosis) continuously and will be increased to 200IU/kg if toxicity is acceptable as defined in the protocol. Patients will be included in the Phase I part of the study in cohorts of three patients. Sunitinib will be given at the standard treatment dose of 50mg daily for 4 weeks followed by a 2 week rest period.

Intervention

Addition of daily subcutaneous Dalteparin injections to standard Sunitinib treatment for patientens with metastatic or inoperable renal cell cancer.

Study burden and risks

Patients will inject themselves with a daily subcutaneous injection of Dalteparin. In addition, approximately 4-5 extra visits to the hospital are required to perform additional investigations and to monitor toxicity of the treatment.
There is a possibility of an increased risk of bleeding caused by the combination treatment. Necessary precautions in in and exclusion criteria as well as detailed dose modification rules are being applied to minimize this additional risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Patients must have histologically confirmed renal cell carcinoma that is metastatic or unresectable.
2) Clear cell and non-clear renal carcinoma patients are eligible. Oncocytoma, collecting duct tumors and transitional cell carcinoma are NOT eligible.
3) No prior systemic treatments for metastatic disease are permitted, including antiangiogenic therapy, immunotherapy, chemotherapy and investigational therapy.
4) Patients with their primary tumor in place who are appropriate surgical candidates should be strongly encouraged to undergo nephrectomy prior to treatment initiation, based on the potential effect on survival.
6) Prior palliative radiation to metastatic lesion(s) is permitted, provided there is at least one measurable and/or evaluable lesion(s) that has not been radiated.
7) Radiation therapy must be completed >4 weeks prior to registration
8) Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension as >20 mm with conventional techniques or as >10 mm with spiral CT scan (RECIST criteria).
9) Age > 18 years.
10) ECOG performance status * 2.
11) Patients must have normal organ and marrow function as defined below:
* leukocytes >3,000/mm3
* absolute neutrophil count >1,500/mm3
* platelets >100,000/mm3
* total bilirubin <1.5 x laboratory upper limit of normal
* AST(SGOT)/ALT(SGPT) <2.5 x laboratory upper limit of normal
* creatinine <1.5 x laboratory upper limit of normal
* PT/INR <1.5
* Urine protein <1+; if >1+, 24 hour urine protein should be obtained and should be <1000 mg
12) The effects of Sunitinib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because angiogenesis inhibitors are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
13) Ability to understand and the willingness to sign a written informed consent document.
14) The effect of this combination treatment on the risk for hemorrhage is unknown, but it is possible that it is increased. Therefore, except for Dalteparin that will be administered as a study drug, the patients should not take any other anticoagulants or anitiplatelet agents during the study, including but not limited to NSAID (any dose of aspirin), warfarin or other anticoagulants.

Exclusion criteria

1) Patients may not be receiving any other investigational agents.
2) Patients with known CNS metastases. Patients should have a head CT/MRI within 14 days prior to treatment initiation. Any imaging abnormality indicative of CNS metastases will exclude the patient from the study.
3) Patients with a *currently active* second malignancy other than non-melanoma skin cancers are not eligible. Patients are not considered to have a *currently active* malignancy if they have completed anti-cancer therapy and are considered by their physician to be at less than 30% risk of relapse.
4) Patients with a large (>2cm) pulmonary lesion involving the trachea or one of the main bronchus and any endobronchial lesion.
5) History of allergic reactions attributed to compounds of similar chemical or biologic composition to Dalteparin.
6) Evidence of bleeding diathesis within last 6 months.
7) Serious or non-healing wound, ulcer or bone fracture or active peptic ulceration.
8) Current therapeutic full-dose of anticoagulants, either warfarin or LMWH or unfractionated heparin.
9) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (New York Association Class II, III, or IV), angina pectoris requiring nitrate therapy, recent myocardial infarction (< the last 6 months), cardiac arrhythmia, history of CVA within 6 months (thrombotic or hemorrhagic), hypertension (defined as blood pressure of >160 mmHg systolic and/or >90 mmHg diastolic on medication), hemorrhagic retinopathy, history of peripheral vascular disease, or psychiatric illness/social situations that would limit compliance with study requirements.
10) Patients with an ejection fraction <50% by MUGA scan are not eligible.
11) Pregnant women are excluded from this study because Sunitinib is an angiogenesis inhibitor agent with the potential for teratogenic or abortion inducing effects.
12) History of abdominal fistula, gastrointestinal perforation or intra-abdominal abcess within 28 days prior to day 1 therapy.
13) Invasive procedures defined as:
-Major surgical procedure, open biopsy, or significant traumatic injury within 6 weeks prior to day 1 therapy.
-Anticipation of need for major surgical procedures during the course of the study.
-Core biopsy within 7 days prior to start therapy.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-12-2011
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fragmin
Generic name:	Dalteparin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sutent
Generic name:	Sunitinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2011
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-002962-37-NL
CCMO	NL30412.029.10