Sunitinib prior to nephrectomy in patients with metastatic renal cell carcinoma and the primary tumor in situ

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A phase II trial whose main objective is to investigate the response rate of the primary tumor following pretreatment with sunitinib

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

Summary

ID

NL-OMON30820

Source
ToetsingOnline

Brief title
Sunitinib in primary metastatic renal cell carcinoma

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Renal and urinary tract therapeutic procedures

Synonym
kidney cancer, renal neoplasm

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: metastatic, nephrectomy, renal cell cancer, Sunitinib

Outcome measures

Primary outcome

The main end point of this study is any objective response in the primary tumor according to RECIST criteria .

Secondary outcome

Cancer specific survival and morbidity, overall response at metastatic sites and duration of metastatic response will be assessed. (Duration of overall survival; duration of hospital stay; percentage of withdrawal from nephrectomy due to sunitinib-related reduction of performance; response at metastatic sites; progression to irresectability of the primary tumor during initial treatment).

Immunomonitoring in the peripheral blood at different time intervals and the primary tumor after nephrectomy.

Imaging with CT and dynamic MRI scan prior to treatment with sunitinib and prior to nephrectomy to identify potential response criteria other than RECIST in association with histopathology.

Study description

Background summary

All present trials with sunitinib involving primary metastatic RCC included patients after nephrectomy. That design was chosen because the preferred treatment of primary metastatic RCC patients was nephrectomy first followed by therapy with interferon alpha to treat the remaining metastases. As a result no

data exist about the response of primary tumors to sunitinib. This is of importance, because cytoreductive nephrectomy may have a different role in medical treatment with tyrosine-kinase inhibitors than with interferon alpha. However, it is known that an impressive number of patients have partial responses of their metastases after sunitinib using RECIST criteria. In a recent phase III trial that was 31 % for sunitinib versus 6 % for interferon alpha. It may therefore be that - potentially - the primary tumors would have had an equally high response rate if they would not have been removed prior to treatment.

Study objective

A phase II trial whose main objective is to investigate the response rate of the primary tumor following pretreatment with sunitinib

Study design

The study is designed as a phase II trial of initial sunitinib followed by nephrectomy in primary metastatic renal cell carcinoma with the primary tumor in situ.
This study is designed to detect a 25 % objective response rate in the primary tumor according to RECIST criteria with an alpha of 0.05 and a power of 80 % using a two-stage minimax design developed by Simon.
First, 22 patients will be treated and if at most 1 response is observed in the primary tumor, the study will be stopped for insufficient activity on the primary tumor. If at least 2 responses are obtained, 18 additional patients will be included to a total of 40 patients. If at least 8 primary tumors of these patients respond the treatment will be declared to have sufficient activity on the primary tumor (alpha=0.05 and 80% power if the response is 25% or more). Otherwise the treatment will be declared not sufficiently active on the primary tumor.

Intervention

After patients have expressed that they are willing to take part in the trial, but before registration, those without a histological diagnosis of clear-cell renal cell cancer will undergo 3 transcutaneous tru-cut biopsies of the primary tumor or alternatively a metastatic lesion after local anesthesia with 1 % lidocaine has been applied.Eligible patients will start with sunitinib at a continuous dose of 50 mg/day for 2 cycles of each 4 weeks with 2 weeks off treatment. Patients who deteriorate during treatment or have to withdraw from sunitinib because of side effects will be excluded from the study treatment and offered second-line treatment (investigators choice) after recovery, followed at three-monthly intervals. At completion of the 2nd treatment cycle of 4 weeks tumor assessments are made and patients admitted for surgery maximally 1 week later. All patients will undergo delayed transabdominal tumornephrectomy with

resection of all encompassable metastases, including those patients with progressive metastases, unless rapid progression leads to a deterioration of performance of WHO 2 or worse. After a 3 weeks rest period postoperative tumor assessments are performed and the medication will be continued as 4/2 regimen until progression.

Study burden and risks

The accepted treatment for primary metastatic renal cell carcinoma is a multimodality approach of surgery and medical treatment. In Europe sunitinib has been registered as first line treatment. The best timing of nephrectomy, surgery either before medical treatment or following medical treatment, is not known.
Therefore, the proposed treatment in this trial does not deviate from the accepted concept of a combination of medical and surgical treatment. The only additional burden is drawing blood for immunological examination and the two dynamic MRI scans.

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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. Histologically confirmed metastatic renal cell cancer of clear-cell subtype with a resectable asymptomatic primary in situ. Unless the diagnosis of a clear-cell subtype has been established after histological examination of a resected metastatic lesion, all patients need to undergo a transcutaneous tru-cut needle biopsy of the primary tumor.
2. Extensive metastatic disease which is defined as 3 or more non-resectable metastases in case of 1 metastatic site, using the RECIST criteria, or 2 or more metastatic sites.
3. Age: 18 to 65 years
4. Life expectancy > 3 months
5. WHO performance status 0 or 1
6. Written informed consent obtained from the patient after having been informed about the objectives of the study and the medication used.
7. Blood counts: Leucocytes > 3.0 x 109/l, platelets > 100 x 109/l, hemoglobin > 6.0 mmol/l.
8. Serum bilirubin, ASAT, ALAT and creatinin within 1.5 times of upper limit of reference values of laboratory.
9. No prior systemic treatment with biological response modifiers, tyrosine-kinase inhibitors, monoclonal antibodies or chemotherapy. Patients who receive local radiotherapy for bone lesions can be included.
10. An intermediate MSKCC risk profile.
11. In women of child-bearing age anticonception is required.
12. Patients should be able to drink 2 to 3 liters per day.

Exclusion criteria

1. Symptomatic primary necessitating nephrectomy. For definition see Inclusion criteria of the protocol.
2. Irresectable primary tumor
3. Patients in whom complete surgical remission can be achieved by removing metastatic sites at nephrectomy or by delayed surgery.
4. Previous nephrectomy
5. Low metastatic burden (2 or less non-resectable metastases at 1 metastatic site)
6. Metastatic RCC to the bone only. Bone metastases are considered truly non measurable.
7. Current cardiovascular disease, hematopoetic, pulmonary, hepatic or renal dysfunction or WHO performance status > 1.
8. Previous immunotherapy, therapy with tyrosine-kinase inhibitors, monoclonal antibodies or chemotherapy.
9. Presence of autoimmune disease, HIV and hepatitis.

10. Corticosteroid and/ or other immunosuppressive therapies.
11. Prior malignancies. In case of NED the period should be > 5 years.
12. Central nervous system metastases.
13. non-clear cell subtype.
14. Poor or good prognosis according to MSKCC risk assessment.
15. Pregnancy, lactation or no anticonception in women of child-bearing age.
16. Inability to drink at least 2 liters per day.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2007
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	sutent
Generic name:	sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-01-2007

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2006-006491-38-NL
CCMO	NL15556.031.06