Randomized Phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma. EORTC 30073 SURTIME

Published: 01-03-2010
Last updated: 04-05-2024

The principal objective of the trial is to investigate whether the sequence of the nephrectomy in patients who receive sunitinib has an effect on patient outcome.

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

Summary

ID

NL-OMON34814

Source
ToetsingOnline

Brief title
EORTC 30073 SURTIME

Condition

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

Synonym
kidney cancer, renal cell carinoma

Research involving

Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC,Pfizer

Intervention

Keyword: metastases, nephrectomy, renal cell carcinoma

Outcome measures

Primary outcome

The duration of progression free survival: the time interval between the date of randomization and the first date of progression (local or distant) or death due to any cause. Progression will be defined according to the RECIST 1.1. In case the patient is still alive without progression, the date of progression/death will be censored at the date of last follow up.
In case of early progression within 4 weeks after surgery, the actual date of progression (if confirmed) will be at week 16 in the immediate arm and week 28 in the deferred arm (see Protocol sections 7.1).

Secondary outcome

* Overall survival

* Morbidity

* Overall response to treatment in the deferred nephrectomy arm including the proportion of patients who become unresectable

* Effect of nephrectomy on early progression in both arms

Study description

Background summary

For patients with RCC and disease confined to the kidney the only effective therapy with a high probability of cure is surgical removal of the primary tumor. Unfortunately, up to 30 % of all patients with renal cell carcinoma have metastatic disease at the time of diagnosis with the primary tumor in situ. Surgery alone is ineffective for the majority of patients with primary metastatic renal cell carcinoma and multiple non-resectable metastases, apart from the few patients who present with solitary metastases in whom surgical complete resection of the lesion in conjunction with nephrectomy may lead to prolonged survival and possibly cure in exceptional cases. Randomized controlled trials (Southwest Oncology Group
(SWOG) S8949 and European Organization for Research and Treatment of Cancer (EORTC) 30947) have shown a small but statistically significant survival benefit of 6 monts for cytoreductive nephrectomy (CN) before immunotherapy with interferon alfa in the treatment of metastatic renal cell carcinoma (mRCC) versusinterferon alpha alone.
Oral tyrosine kinase inhibitors targeting VEGF and platelet-derived growth factor (PDGF) receptors have altered the systemic treatment of mRCC. Compared with cytokine therapy sunitinib at a dose of 50 mg daily for 4 weeks on and 2 weeks off induces a high partial response (PR) rate of up to 40% at metastatic sites. Sunitinib is standard of treatment for clear cell subtype, which comprise 70-80 % of all mRCC, but not necessarily standard for other cell types. Sunitinib was evaluated in a phase III trial of 750 patients with largely good- or intermediate-prognosis metastatic clear cell RCC who had not received prior systemic treatment. The objective response rate was significantly increased with sunitinib (39 versus 8 percent with IFNa). Median PFS was significantly prolonged (11 versus 5 months, hazard ratio [HR] 0.54). This benefit included patients at good, intermediate, and poor risk (PFS 14.5 versus 7.9, 10.6 versus 3.8, and 3.7 versus 1.2 months, respectively). Based on this pivotal trial, sunitinib was registered in the US and Europe in 2007 for the treatment of metastatic RCC and became the approved first-line therapy for all patients including patients with primary tumors in situ.
Many centers perform immediate nephrectomy followed by the approved first-line drug sunitinib as the new standard.
In summary, there is evidence that mRCC patients with a good performance, good and intermediate MSKCC risk, low risk of surgery and a clear cell subtype receiving sunitinib as approved systemic treatment may benefit from CN. However, despite these selection criteria, individual prediction of a CN benefit remains elusive. Studies should be designed to identify those individuals in whom CN alters the natural history of mRCC. Identification would require understanding of new clinical and molecular predictors. Therefore, there is a rationale for deferred nephrectomy following targeted therapy and investigation of pretreated primary tumor tissue. In addition, deferred

nephrectomy may improve the clinical outcome.
Recently cases have been described in which the surgical management in advanced RCC was altered by pretreating the tumor in situ with targeted agents. Experience from phase II trials investigating deferred surgery after targeted therapy in renal and other tumors suggest that sunitinib discontinued at least 24 hours prior to surgery is safe. The effect of downsizing the primary tumor is most prominent in the first two to three months suggesting that two to three presurgical cycles of sunitinib may be sufficient. In renal and other cancers, a few days of treatment with tyrosine kinase inhibitors have been shown in patients and animal models to induce a maximal inhibition of cell proliferation and induction of apoptosis.

Study objective

The principal objective of the trial is to investigate whether the sequence of the nephrectomy in patients who receive sunitinib has an effect on patient outcome.

Study design

This is a randomized multicenter phase III comparison trial. Eligible patients will be randomized between immediate versus deferred nephrectomy.

Intervention

Arm A will undergo immediate nephrectomy followed by standard medical treatment for metastatic renal cell carcinoma and compared to arm B in which nephrectomy is deferred until after 3 courses of standard medical treatment for mRCC.

Study burden and risks

Accepted treatment of mRCC is a combination of surgery and medical treatment. The sequence is unknown, but treatment with sunitinib and the techniques of nephrectomy are well established, therefore the trial treatment does not deviate from standard treatment with the exception of serum collection and an additional restaging CT scan.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier, 83/11
Brussels 1200

BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounier, 83/11
Brussels 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically confirmed metastatic Renal Cell Cancer of clear-cell subtype with a resectable asymptomatic in situ primary.
- Metastatic RCC (mRCC): metastases are not completely resectable at the time of surgery or during an additional intervention. Multiple lesions at one site will make the patient not eligible for complete resection.
- Histology *clear-cell* subtype: If the diagnosis is not established patients need to undergo a transcutaneous tru-cut needle biopsy of the primary tumor.
- Resectable tumor: primary tumor must be resectable and resectability should not be doubtful at entry. Patients with distant metastases and bulky locoregional lymph node metastases larger than the primary tumor can be included if resectability of the lymph nodes is surgically feasible.
- Asymptomatic primary: is defined as the absence of symptoms which can be exclusively assigned to the primary tumor such as flank pain and/or gross hematuria necessitating blood transfusion. As para-neoplastic symptoms cannot be assigned to the primary tumor alone in metastatic disease, they are not included in this definition.
- Patients who will receive Sunitinib (Sutent®) as background therapy.
- Measurable disease according to RECIST 1.1 criteria.
- Prior therapies:
- Prior systemic therapy for metastatic RCC is not allowed

- Prior local radiotherapy for bone lesions is allowed
- Concomitant medications:
- Investigational or systemic therapy for metastatic RCC must not be used during the period of protocol treatment.
- No systemic corticosteroid and/ or other immunosuppressive systemic therapies
- Age * 18 years.
- Life expectancy > 3 months.
- WHO performance status 0 or 1.
- Adequate bone marrow function (Leucocytes > 3.0 x 109/l, platelets >100 x 109/l, hemoglobin > 6.0 mmol/l or > 10.0 g/dL.)
- Prothrombin time (PT) or international normalized ratio (INR) * 1.2 x upper limit of normal (ULN).
- Partial thromboplastin time (PTT) * 1.2 x ULN.
- Adequate hepatic function (bilirubin * 1.5 x ULN, SGPT/ALT * 2.5 x ULN or * 5 x ULN if liver lesions).
- Serum calcium < 10.0 mg/dL.
- Adequate renal function: calculated or measured clearance creatinine >30 ml/min.
- Clinically normal cardiac function based on the institutional lower limit of normal LVEF assessed by MUGA or ECHO and normal 12 lead ECG.
- Patients with any history of malignancies who are disease-free for more than 5 years are eligible.
- Women must be post-menopausal with a total cessation of menses of >1 year, or if of childbearing potential must not be pregnant (negative serum pregnancy test at entry) or lactating; and must agree to use effective contraceptive methods (with a documented failure rate < 1% e.g.; vasectomized partner sterile prior to trial entry and sole sexual partner or double-barrier contraception) from 2 weeks before to enrollment. The duration of the contraception will depend on the treatment that patient will receive.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial.
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

- Patients for whom complete surgical remission can be achieved by removing metastatic sites at nephrectomy or during an additional intervention.
- Patients with symptomatic primary necessitating nephrectomy.
- Patients with previous partial or total nephrectomy.
- Patients with unresectable bulky locoregional lymph node metastases larger than the primary tumor.
- Patients with only bone metastases.

- Patients having more than 3 of the following surgical risk factors will not be eligible:
- serum albumin CTCAE v4.0 grade 2 or worse
- serum LDH > 1.5 x UNL
- liver metastases
- symptoms at presentation due to mestastases
- retroperitoneal lymph node involvement
- supra-diaphragmatic lymph node involvement
- clinical stage T3 or T4
- Patients with serious cardiac illness (myocardial infarction and/or (un)treatable angina pectoris not responding to treatment) within the past 12 months.
- Uncontrolled high blood pressure (BP) defined as BP * 150/100 mm Hg despite optimal medical therapy.
- Clinical signs of CNS involvement.
- Current pulmonary disease.
- Patients with active or uncontrolled infections or with serious illnesses, malabsorption syndrome or medical conditions, including patients with a history of chronic alcohol abuse, hepatitis, HIV and/or cirrhosis.
- History, within the past five years, of malignancies other than renal cell carcinoma (except: basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, resected incidental prostate cancer staged pT2 with Gleason Score * 6 and postoperative PSA < 0.5 ng/ml).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-07-2010
Enrollment:	147

Type:	Actual

Ethics review

Approved WMO Date:	01-03-2010
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
CCMO	NL29931.031.09