Phase I dose-escalation trial for the combination of sorafenib with interleukin-2 (IL-2) in patients with clear cell renal cancer

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Objectives Primary end point:- to define the MTD of IL-2, subcutaneously given once a day, 5 days per week, for 6 weeks, in combination with a fixed dose of sorafenib in patients with metastatic RCC, clear cell subtype. Secondary end points:- the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON30060

Source
ToetsingOnline

Brief title
M06SIL

Condition

- Metastases
- Ureteric disorders

Synonym
kidney cancer; renal cancer

Research involving
Human

Sponsors and support

Primary sponsor: NKI-AVL
Source(s) of monetary or material Support: Bayer,bedrijf

Intervention

Keyword: IL-2, Phase I, renal cell cancer, sorafenib

Outcome measures

Primary outcome

Only patients who start concurrent IL-2 treatment are evaluable for this study.

If treatment with sorafenib during the first 4 weeks has to be stopped,

interrupted or adjusted because of dose-limiting toxicity (DLT) (see for

definition of DLT below) or other reasons, patients will go off-study and will

be replaced. In these cases, patients are allowed to continue treatment with

sorafenib according to the treating physician*s opinion.

Adverse events that are encountered during the first cycle when IL-2 is

co-administered (6 weeks) will be used to guide dose escalation and to define

the MTD. Adverse events will be graded according to the NCI-CTC version 3.0.

Dose-limiting toxicity (DLT) will be defined as those adverse advents that are

considered possibly, probably, or definitely related to the study drugs.

DLT is defined as:

- grade 4 neutropenia or grade 4 thrombopenia

- grade 3 or greater non-hematologic adverse events except fever, rigor/chills,

renal dysfunction, hypertension, nausea/vomiting, diarrhea, and fatigue for

which the following criteria will apply:

o fever or rigor/chills of any grade will not be considered DLT

o creatinine >= 2 x ULN

o hypertension with systolic blood pressure >= 160 mmHg and/or diastolic blood pressure >= 100 mmHg lasting longer than 14 days despite adequate treatment

o grade 3 or greater persistent (more than 7 days) nausea/vomiting despite adequate treatment or prophylaxis

o grade 3 or greater (more than 7 days) diarrhea despite adequate treatment or prophylaxis

o grade 4 fatigue

At each dose level, at least 3 patients will be treated. Patients in each dose level will be treated for 4 weeks with sorafenib (400 mg bid) (run-in period). After this, IL-2 will be administered at the designated dose for that dose level. When each patient of the first three entered patients in a particular dose level has had 6 weeks of treatment with the combination of sorafenib and IL-2 without a DLT, the IL-2 dose will be escalated in the next cohort. In case a single patient of the first three patients at a dose level encounters DLT, then that dose level will be expanded to 6 patients. If no more DLTs occur in the additional three patients (in total 1 DLT/6 patients), then the IL-2 dose will be escalated in the next cohort. In case a total of two or more DLTs develop in the first 6 patients of a cohort, then this dose level is declared the toxic dose. The dose level below the toxic dose or the maximum dose level explored will be expanded to a total of 10-12 patients to get more insight in

the exact toxicity profile and will be declared the maximum tolerated dose (MTD) if the final DLT rate is < 33%.

Secondary outcome

Pharmacokinetics:

To assess whether concurrently administered IL-2 affects pharmacokinetics of sorafenib, systemic blood levels of sorafenib will be determined at the end of the run-in period at day 29 prior to the first administration of IL-2 alone when sorafenib is given as single agent and at day 5 after starting IL-2 sc.
Per time point 20 ml will be sampled.

Cytokines:

To assess the effects of sorafenib as well as of the combination of sorafenib and IL2 on VEGF and interleukin-6 (IL-6) levels in the peripheral circulation, 20 ml peripheral blood (serum) will be sampled at:
Base-line, day 29 run-in period prior to the first administration of IL-2, day 5 after start concomitant IL-2, day 43 after start concomitant IL-2.

Peripheral blood cells:

To assess the effects of sorafenib as well as of the combination of sorafenib and IL2 on peripheral blood cells (NK-cells (CD56+, CD3-), Cytotoxic T-cells (CD3+, CD8+), T-helper cells (CD3+, CD4+), Regulatory T-cells (CD3+, CD4+, CD25bright/Foxp3)), 30 ml blood (EDTA/heparin) will be sampled at:
Base-line, day 29 run-in period prior to the first administration of IL-2, day

5 after start concomitant IL-2, day 42 after start concomitant IL-2.

Study description

Background summary

Renal cell carcinoma is a relatively rare tumor type accounting for approximately 1500 new cases each year in The Netherlands, of which the clear cell subtype is the most predominant one. The vast majority of patients presents with localised disease, but dependent on stage at presentation many of these patients experience metatastic disease later on. For these and for those patients initially diagnosed with metastatic disease systemic treatment is indicated.
Until recently, the only available treatment option for patients with metastatic RCC was cytokine-based treatment with interferon-α (IFN-α) or interleukin-2 (IL-2) containing regimens. It has been shown that only patients with advanced RCC from the clear cell subtype benefit from cytokine-based treatment, while patients with other tumor subtypes such as the chromophobic or papillary subtype do not. Therefore, IFN-α or IL-2 based regimens have been considered standard treatment for patients presenting with advanced clear cell RCC with only few durable complete responses.
Recently, novel compounds have been developed inhibiting VEGF-R mediated effects by targeting the tyrosine kinase domain of the VEGF-R, which is essential for signal transduction of this receptor. One of these drugs is sorafenib, which has recently been explored for its anti-tumor activity in clear cell RCC. In a randomised, placebo-controlled trial in patients with progressive disease after first line cytokine-based treatment, sorafenib improved both progression-free and overall survival as compared to placebo at the expense of an acceptable toxicity profile.
The combination of IL-2 and a VEGF-R tyrosine kinase inhibitor such as sorafenib is a theoretically promising regimen in patients with advanced clear cell RCC. Next to the fact that both sorafenib and IL-2 exhibit anti-tumor activity against this tumor entity, synergistic activity may be expected when these two drugs are concurrently applied.

Study objective

Objectives
Primary end point:
- to define the MTD of IL-2, subcutaneously given once a day, 5 days per week, for 6 weeks, in combination with a fixed dose of sorafenib in patients with metastatic RCC, clear cell subtype.

Secondary end points:

- the effect of IL-2 co-administration on plasma sorafenib pharmacokinetics.
- to evaluate disease response according to RECIST criteria and time to progression.
- to establish the effect of treatment on immune cell populations and cytokines.

Study design

This is a clinical phase I dose escalation study in metastatic clear cell renal cancer patients with sorafenib and subcutaneous IL-2.

Intervention

All patients will be continuously treated with a fixed dose of sorafenib, 400 mg bid. If after 4 weeks of sorafenib treatment (run-in period), patients have no signs of progressive disease and tolerate sorafenib well, IL-2 will be added according to pre-defined dose cohorts with 3-6 patients per cohort.

Initial dose level:
During the first week 9 MU per day, in the subsequent 5 weeks the first two days 4.5 MU per day followed by 9 MU per day for the remaining 3 days.

If the initial dose level is not the toxic dose, then the next and highest dose level will be:
During the first week 18 MU per day, in the subsequent weeks the first two days 9 MU per day followed by 18 MU per day for the remaining 3 days.

If the initial dose level is the toxic dose, then the next and lowest dose level will be:
During the first week 4.5 MU per day, in the subsequent weeks the first two days 2.25 MU per day followed by 4.5 MU per day for the remaining 3 days.

Study burden and risks

For patients with advanced-stage renal cell cancer no curative treatment exists except high-dose IL-2 that results in durable complete remissions in 7-8% of cases. Also treatment with the new oral receptor tyrosine kinase inhibitors, such as sorafenib and sunitinib, have not been shown to result in complete remissions. Therefore, more research is required to improve the treatment of these patients. The combination of sorafenib and IL-2 is potentially more active than the drugs alone. Since this combination has not been tested before, but both drugs are registered for treatment of advanced-stage RCC, a phase I study is needed to define the toxicity and maxium tolerated dose of IL-2 in combination with flat dose sorafenib.
The examinations required for participation in this trial are standard and the

extra blood sampling is not considered a heavy burden for these patients.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients with cytologically or histologically proven RCC, clear cell subtype, with documented progressive disease either after first line, interferon(IFN)-α- or interleukin-2-based therapy or for whom IFN-α-based treatment is not considered appropriate because of prognostic features according to Motzer.
- Evaluable and measurable disease (according to RECIST criteria)
- PF 0-1
- Adequate bone marrow, hepatic and renal function
- life expectancy of at least 3 months
- age of 18 or older

- willingness to use a medically approved method of contraception
- before patient randomization, written informed consent must be given and documented to ICH/EU GCP, and national/local regulatory requirements and the local rules followed in the institution

Exclusion criteria

- Uncontrolled or poorly controlled hypertension (systolic blood pressure >= 150 mmHg, diastolic blood pressure >= 90 mmHg). Initiation or adjustment of blood pressure medications is permitted prior to study treatment provided that 3 consecutive blood pressure readings are <= 150/90 mmHg, each separated by at least 24 hours
- Concurrent therapy with prohibited medication
- History of malabsorption syndrome or other disease that could significantly affect absorption of drugs
- Other malignancies (previous or current), except adequately treated basal or squamous cell carcinoma of the skin and carcinoma in situ of breast or cervix
- Prior treatment with VEGF or VEGF-R targeting agent (monoclonal antibody or tyrosine kinase inhibitor)
- Cytotoxic, hormonal, investigational treatment or immunotherapy within 4 weeks prior to day 1 of study treatment
- Major surgery within 4 weeks prior to study treatment
- Persistent grade 2 or greater toxicity related to prior treatment (except alopecia) (NCI-CTC version 3.0)
- History of any infection requiring hospitalisation or antibiotics within 2 weeks prior to study treatment
- Systemic steroids within 2 weeks prior to study treatment
- Myocardial infarction or cerebrovascular accident (CVA) within 6 months prior to study treatment
- Congestive heart failure requiring medication
- Known brain metastases
- Known human immunodeficiency virus (HIV) infection
- Known chronic or acute viral hepatitis
- Pregnant or breast-feeding women.

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):	20-11-2006
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Proleukin
Generic name:	interleukin-2
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	02-10-2006
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	16-11-2006
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	EUCTR2006-004010-40-NL
CCMO	NL13627.031.06