A phase I study of the combination of daily oral SU11248 (Sunitinib) with intravenous ifosfamide in patients with advanced solid malignancies.

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To evaluate the safety and tolerability of escalating doses of oral sunitinib in combination with standard doses of intravenous ifosfamide in patients with solid malignancies.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON30366

Source
ToetsingOnline

Brief title
SU11248/Ifosfamide

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
solid advanced tumors

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Grant van de farmaceutische industrie,Pfizer

Intervention

Keyword: ifosfamide, Phase I, Solid malignancies, sunitinib

Outcome measures

Primary outcome

Determination of the maximum tolerated dose (MTD) and dose-limiting toxicity

(DLT) of sunitinib when given in combination with standard doses of ifosfamide.

Secondary outcome

To determine the impact of sunitinib on ifosfamide pharmacokinetics and vice

versa.

To evaluate the impact of this combination on surrogate markers including VEGF

and soluble VEGF-R plasma levels and the number of circulating endothelial

cells (CECs)

To record any disease response

Study description

Background summary

The use of so-called targeted drugs, such as monclonal antibodies and tyrosine kinase inhibitors is rapidly increasing in oncology. In particular in combination with conventional chemotherapeutic drugs, the appliation of these new drugs is attractive for several reasons.
Sunitinib is an inhibitor of the tyrosine kinases responsible for the signal transduction of several proteins including c-kit and the receptors for Vascular Endothelial Growth Factor (VEGF-R) and the Platelet Derived Growth Factor (PDGF-R). Inhibition of these receptors by sunitinib leads to a well-established antitumor effect in patients with gastrointestinal stroma tumor and renal cell cancer. An antitumor effect can also be anticipated in other tumor types which have a VEGF or PDGF mediated growth, such as soft tissue sarcomas, testicular cancer and CNS tumors.
Ifosfamide is a one of the oldes chemotherapeutic agents and it is used in the treatment of various tumor types.

A synergistic antitumor activity can be anticipated using sunitinib in combination with ifosfamide since sunitinib can decrease chemoresistance by inhibiting the production of anti-apoptotic proteins such as Bcl-2 and survivin. Furthermore, it has been shown that conventional cytotoxic agents induce VEGF production by tumor cells in vitro, and that increased VEGF tumor levels are a predictive factor for poor outcome on systemic treatment in humans. Since sunitinib inhibits both PDGF and VEGF-mediated activities, it can be anticipated that co-treatment with sunitinib will render tumor cells more prone to apoptotic triggers such as conventional chemotherapy.

Study objective

To evaluate the safety and tolerability of escalating doses of oral sunitinib in combination
with standard doses of intravenous ifosfamide in patients with solid malignancies.

Study design

A Phase I study with a classic 3+3 design. Three different dose cohorts of daily sunitinib (12.5mg, 25mg and 37.5mg) will be evaluated in combination with a fixed dose ifosfamide iv(3g/m2/day for three days) administered at 3-weekly intervals. After establishing the MTD with the 3-day ifosfamide regimen, this MTD of sunitinib will also be evaluated with ifosfamide iv at 1.2g/m2/day for 5 days.

Intervention

not applicable

Study burden and risks

nvt

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

- Histologically or cytologically proven advanced solid malignancy in patients for whom no better treatment than SU11248 and ifosfamide is available.
- Measurable (according to RECIST criteria) or evaluable disease.
- At least 4 weeks since any prior anti-tumor therapy and resolution of all toxicities induced by this prior anti-tumor treatment to CTC grade <= 1 (if not specified below) except alopecia.
- Age >= 18 years.
- WHO performance of 0-1 and a predicted life expectancy of at least 3 months.
- Adequate organ function defined as follows:
serum bilirubin <= 1.5 x ULN
serum AST and ALT <= 2.5 x ULN (in case of liver metastases, then AST/ALT must be <= 5 x ULN)
serum creatinine <= 1.5 x ULN creatinine clearance >= 60 ml/min and 2 functioning kidneys
ANC >= 1.5 x 109/L
platelets >= 100 x 109/L
hemoglobin >= 6.0 mmol/L
- Systolic blood pressure lower than 150 mmHg and diastolic blood pressure lower than 90 mmHg (treatment with 2 antihypertensive drugs is allowed)

Exclusion criteria

- severe/unstable angina or symptomatic congestive heart failure within 12 months prior to inclusion
- myocardial infarction, or cerebrovascular accident within 12 months prior to inclusion

- atrial fibrillation of any grade or ongoing cardiac dysrhythmias >= grade 2
- known human immunodeficiency virus (HIV) positivity
- use of prohibited co-medication as mentioned in paragraph 5.4
- pregnancy and / or breast feeding; for all women of child-bearing potential a negative pregnancy test will be required as well as the willingness to use adequate contraception during the study until 4 weeks after stopping treatment.
- signs or symptoms of CNS metastases (radiological assessment of potential CNS metastases is not required).
- 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.
- other severe medical or psychiatric conditions that in the judgment of the investigator renders the patient inappropriate for inclusion in this study.

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):	02-05-2007
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ifosfamide
Generic name:	Ifosfamide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sutent

Generic name:	Sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-12-2006
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-10-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2006-005188-25-NL
CCMO	NL14454.078.06