The vascular and metabolic effects of sunitinib in patients with metastatic renal cell carcinoma

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The primary objective of the study is to investigate the effect of sunitinib on endothelial function, insulin sensitivity, renal function and renal blood flow.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON34257

Source
ToetsingOnline

Brief title
SUMAVA

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Renal and urinary tract neoplasms malignant and unspecified
- Vascular hypertensive disorders

Synonym
elevated blood pressure, Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: Endothelial function, Hypertension, Insulin sensitivity, Sunitinib, Tyrosine kinase inhibitors

Outcome measures

Primary outcome

In group A: forearm vasomotor response to increasing doses of intra-arterially administered acetylcholine and nitroglycerine before and after start of treatment with sunitinib.

In group B: insulin sensitivity measured by hyperinsulinemic euglycemic clamp before and after start of treatment with sunitinib.

In group C: GFR and RPF measured by PAH and inulin clearance before and after start of treatment with sunitinib.

Secondary outcome

1. To investigate the effect of sunitinib on body weight and blood pressure

2. To investigate the effect of sunitinib on levels of VEGF, soluble VEGFR, renin, aldosteron, endothelin-1 and renal function in relation to blood pressure

3. To investigate the effect of sunitinib on levels of glucose, total cholesterol, HDL, LDL, triglycerides, insulin, C-peptide, IGF-I, pro-IGF-II, TSH, FT4, leptin, ghrelin, adiponectin, IL-6, IL-18, TNF-α, IFN-γ.

4. To investigate the effect of oral daily sunitinib dosing on insulin requirement in the diabetic subpopulation.

Study description

Background summary

Hypertension

Decreased production of nitric oxide (NO) seems to be part of the mechanism inducing hypertension in patients treated with angiogenesis inhibitors. NO causes vasodilatation, inhibits proliferation of vascular smooth muscle cells and diminishes endothelial adhesion of platelets and leucocytes. Decreased NO synthesis promotes vasoconstriction, increases peripheral resistance, decreases renal excretion of sodium ion and increases blood pressure 1. One of the main targets of angiogenesis inhibitors is vascular endothelial growth factor (VEGF). VEGF plays an important role in the proliferation of new blood vessels necessary for tumor growth 2, 3. In animal experiments, VEGF induces hypotension due to synthesis and/or release of NO 4. In human umbilical vein endothelial cells treatment with VEGF resulted in both an acute (1 h) and chronic (>24 h) stimulation of NO production 5. In animal experiments it is shown that vasodilator properties of endogenous VEGF may play a role in normal vascular tone. Theoretically inhibition of VEGF or VEGFr in humans would decrease NO production and thereby induce vasoconstriction and hypertension.
Another proposed mechanism of angiogenesis inhibitor-induced hypertension is vascular rarefaction, which is a reduction in the density of micro vessels. Rarefaction is a normal component of aging and has been demonstrated to occur to a greater degree in hypertensive adults.
Other possible factors contributing to elevated blood pressure in patients treated with angiogenesis inhibitors are adrenergic, renal or renovascular mechanisms.
The appearance of hypertension, particularly grade 3, was associated with higher treatment response to sunitinib in metastatic Renal Cell Carcinoma (mRCC)6. Discontinuation of treatment with sunitinib because of hypertension should therefore be avoided and early and adequate treatment of elevated blood pressure seems to be essential. Moreover, insight in the pathogenesis of this side effect could give us insight in how these angiogenesis inhibitors affect the tumor and thereby give us opportunities to optimize this type of therapy.
The pathogenesis of hypertension caused by treatment with angiogenesis inhibitors remains unclear. Understanding the pathogenesis of this type of hypertension is essential for optimal treatment with antiangiogenic therapy.
In a retrospective study of 200 patients with metastatic renal cell carcinoma
It has been described that sunitinib lowers blood glucose levels, even so that in a diabetic patient blood glucose lowering medication could be withdrawn 8. A non-significant decrease of IGF-1 was observed at week 4 in five diabetic patients. Moreover for sunitinib, a case of a patient with diabetes mellitus type 1 and renal cell carcinoma with a decrease in insulin requirements has been reported9.
This could imply that sunitinib could reduce insulin resistance, possibly by interfering with the IGF-1 pathway. Alternatively, intestinal toxicity could have reduced absorption of oral glucose reducing the need for glucose lowering drugs. Systematically prospective research regarding the effect of angiogenesis inhibitors on insulin resistance has not yet been performed.

Study objective

The primary objective of the study is to investigate the effect of sunitinib on endothelial function, insulin sensitivity, renal function and renal blood flow.

Study design

Single-centre non randomized observational study

Study burden and risks

Patients will not benefit from participating in this study. The intentional treatment of their disease, i.e. treatment with sunitinib, will not change. In group A plethysmography will cause numbness and discomfort in both hands due to inflation of the wrist-cuffs. This is temporarily and completely reversible.
Sometimes there can be some numbness or tingling of fingers due to a hematoma caused by the intra-arterial cannule for a few weeks after the experiment.
Finally in Group A/B/C, bruising may occur after venapuncture or removal of the intra-arterial 27 G needle. Measures like pressure bandage will be taken to minimize the risk.
Side effects due to the euglycemic hyperinsulinemic clamp or PAH/inuline clearance are infrequent.

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

• Subject is able and willing to sign the Informed Consent Form
• Age 18 years or older
• WHO performance status 0-2
• Life expectancy >= 12 weeks
• mRCC patients in which the treatment of choice is sunitinib

Exclusion criteria

1) Use of corticosteroids
2) Any evidence of severe or uncontrolled diseases other than renal cell carcinoma eg, unstable or uncompensated respiratory, cardiac, hepatic or renal disease.
3) Known risk of the patient transmitting HIV, hepatitis B or C via infected blood
4) Patients being treated with oral anticoagulants if to be included in group A.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	01-11-2010
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	20-08-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL33069.091.10