Identification of biological effects of bevacizumab in surgically resectable melanoma tumors.

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To identify biological effects of bevacizumab therapy and to visualize distribution kinetics of 111In-bevacizumab with gamma-camera imaging.

Ethical review	Approved WMO
Status	Pending
Health condition type	Skin neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON30987

Source
ToetsingOnline

Brief title
Identification of biological effect of bevacizumab in melanoma patients

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma cancer, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF,roche (unrestricted grant)

Intervention

Keyword: bevacizumab, imaging, melanoma

Outcome measures

Primary outcome

Safety assessments will consist of evaluating labatory parameters and adverse

events according to NCI CTCAE 3.0.

The following variables will be analyzed to assess the effectiveness of

bevacizumab in the treatment of melanoma tumors:

• Biological parameters.

• Histopathological parameters.

• 111In-bevacizumab distribution kinetics by gamma-camera imaging.

Secondary outcome

n.a.

Study description

Background summary

1.1 Melanoma
Malignant melanoma is an important cause of morbidity and mortality. The 5 year survival in patients with a local recurrent malignant melanoma is less than 50%. The tumor is relatively chemotherapy resistant. Dacarbazine (DTIC) is accepted generally as therapy in metastatic disease with a response rate of approximately 20%, though without significant impact on survival. Biochemotherapy, combining chemotherapeutic drugs with interleukin or interferon has not been proven to be superior to single agent DTIC. Apart from chemotherapy, molecular targeted therapy has emerged in the treatment of tumors. One of these monoclonal antibodies, bevacizumab (Avastin®), has been approved by the FDA for clinical use in metastatic colorectal disease.
Currently, several studies have been started in which the use of bevacizumab is evaluated, with or without the use of single or combined chemotherapy in patients with melanoma tumors.

Overexpression of VEGF and the VEGF receptor occurs in > 80 % of the malignant melanoma. At this time, it is unknown whether patients with malignant melanoma will respond to bevacizumab therapy.

1.2 Angiogenesis
There are several factors involved in the development and growth of tumors. Angiogenesis, the forming of new blood vessels is one of these factors. New vasculature allows tumor cells to execute their critical growth by supplying the tumor with nutrients and oxygen, disposal of metabolic waste products and provides route for metastatic spreading. An important factor involved in angiogenesis is VEGF 5. VEGF is released by tumor cells and induces tumor neovascularization. VEGF consists of at least 4 splice variants, containing 121, 165, 189 and 206 amino acids 5, involved in endothelial proliferation, tubular formation, endothelial survival, endothelial migration, vascular permeability and gene expression. These actions are thought to be transmitted by the VEGF-receptors VEGFR-1, VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4). The VEGF-receptors are tyrosine kinase mediated transmembrane receptors. The VEGF production is thought to be regulated by hypoxemia, cytokines and cell differentiation.
Over-expression of VEGF occurs in many human tumor types. The local VEGF production leads to paracrine effects in the tumor, resulting in angiogenesis and growth exploration. This has lead to interest in blocking the signaling of VEGF in human tumors. Chemical molecules which can block the tyrosine kinase function of VEGF-receptors and antibodies binding to the ligand and the receptor have been developed.
An example is the monoclonal antibody bevacizumab which is derived from the murine VEGF monoclonal antibody A4.6.1. It blocks VEGF induced endothelial cell proliferation, permeability and survival, and it inhibits human tumor cell line growth in nude mice. The likely mechanism of its anti-angiogenic activity is that soluble VEGF is prevented from binding to its receptors, thereby blocking the biological pathways of VEGF.

Study objective

To identify biological effects of bevacizumab therapy and to visualize distribution kinetics of 111In-bevacizumab with gamma-camera imaging.

Study design

Observational study evaluating the anti-angiogenic and apoptotic response of bevacizumab in patients with surgically resectable melanoma.
Patients with surgically resectable melanoma, who are planned for surgery will be treated neo-adjuvant with bevacizumab therapy. The anti-angiogenic and apoptotic response will be evaluated by measuring hematological and histological parameters. The distribution kinetics of 111In-bevacizumab will be visualized by gamma-camera imaging. The patients will receive two injections of

111In-bevacizumab and four gamma-camera scans. The first 2 scans will serve as a baseline. After the second scans it will be possible to compare imaging data before and after treatment and hereby evaluate tumor response.

Study burden and risks

In this study bevacizumab is administered in both therapeutic dose and in tracer-dose, therefore the risk of side-effects is present. The risk of any additional side effects by the administration of a tracer dose (10 mg) of radiolabeled bevacizumab will be very low, compared to therapeutic administration of bevacizumab (375-600 mg).
The most common side-effects reported after first line bevacizumab therapy are diarrhea, hypertension, thrombotic events, deep thromboplebitis, pulmonary embolus, bleeding, proteinuria and gastro-intestinal bleeding. These events are for the most part mild to moderate in severity and clinically manageable (hypertension, proteinuria, minor bleeding) or occur uncommonly (wound healing complications, GI perforations and arterial thrombosis). Whether or not a single dose of bevacizumab can induce any adverse effect is uncertain. Any toxicity will be scored according to the Common Toxicity Criteria version 3.0. Patients will be informed about possible side-effects and have physical examination routinely.

Administration of 111In-bevacizumab entails radiation load from the participating patients. It has been calculated that a dose of 100 Mbq will lead to a radiation load of 18mSv (see appendix 13.3). In this study protocol this will lead to 36 mSv. For comparison, a CT-abdomen will lead to a radiation dose of 10-15 mSv. The poor prognosis of this patient group (5 year survival < 50%) and the potential new information given by this study makes this radiation load acceptable.

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

• Surgically resectable melanoma.
• WHO performance status 0-2.
• Age >18 years.
• Minimum required laboratory data:
• Hematology: Leucocytes 4,0-10,0x109/l.
• Biochemistry: bilirubin < 1.5 x upper normal limit. Serum creatinine within normal limits INR < 1.5.
• Before patient registration/randomization, written informed consent must be given according to national and local regulations.
• Able to comply with the protocol

Exclusion criteria

• Prior chemotherapy or biological therapy for metastatic disease.
• Prior radiotherapy on the involved area.
• Major surgery within 28 days before the initiation of the study.
• Clinically significant cardiovascular disease.
• Pregnant or lactating women. Documentation of a negative pregnancy test must be available for pre-menopausal women with intact reproductive organs and for women less than two years after menopause.
• CNS metastases (CT-Scan not mandatory).
• Treatment with any investigational drug within 30 days before the start of the study.
• Prior allergic reaction to immunoglobulins or immunoglobulin allergy.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2007
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Generic name:	111In-bevacizumab
Product type:	Medicine
Brand name:	Bevacizumab
Generic name:	Avastin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2007-001470-83-NL
CCMO	NL17111.042.07