

Molecular imaging with radiolabeled bevacizumab in metastatic colon carcinoma.

A feasibility study in patients who do show response on bevacizumab therapy

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To recognize the distribution pattern of ¹¹¹In-bevacizumab in patients who show response on treatment with bevacizumab. The ultimate goal is to identify and select patients who can be successfully treated.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON30912

Source

ToetsingOnline

Brief title

Molecular imaging with radiolabeled bevacizumab in colon carcinoma

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym

colon 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, colon cancer, imaging

Outcome measures

Primary outcome

Safety assessments will consist of evaluating laboratory 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 metastatic colon carcinoma:

- Biological parameters.
- ¹¹¹In-bevacizumab distribution kinetics by gamma-camera imaging. Evaluation of gamma-camera imaging to recognize the distribution pattern of ¹¹¹In-bevacizumab in patients who do show response to bevacizumab therapy.

Secondary outcome

n.a.

Study description

Background summary

1.1 Treatment of metastatic colon rectal carcinoma (CRC)

For a long time, 5-fluorouracil (5-FU) has been the only proven treatment for colorectal cancer. 5-FU treatment was generally combined with leucovorin. Novel cytotoxic agents have expanded the treatment options. New compounds like irinotecan, oxaliplatin and capecitabine have been implicated. Co-administration of first irinotecan and secondly oxiplatin to 5-FU/leucovorin (FOLFOX-regime) lead to increased patients survival. These data have caused

that the FOLFOX regime was approved as first-line chemotherapy for metastatic CRC.

Although these new drugs lead to increased survival, the poor prognosis of metastatic CRC have encouraged the development of new drugs, preferably with minimal toxicity. Recently, new drugs have been developed, targeting different pathways which are known to drive tumor progression. Some of these drugs, like trastuzumab have shown clinical benefit in for example breast cancer.

Another example is bevacizumab (Avastin®) which is a humanized monoclonal antibody designed to inhibit vascular endothelial growth factor (VEGF), the key mediator in angiogenesis. In the first phase III trial, bevacizumab was combined with first line chemotherapy IFL (irinotecan, 5-FU and leucovorin) in the treatment of CRC. Bevacizumab was i.v. administered once every two weeks in a dose of 5 mg/kg. The primary endpoints were significantly increased. The overall survival improved from 15.5 to 20.3 months ($p < 0.001$). Patient disease free survival increased from 6.2 to 10.6 months ($p < 0.001$). The overall response rate increased from 34.8% to 44.8% ($p = 0.004$) in the arm treated with bevacizumab compared to the IFL/placebo arm. This benefit was seen in all patient groups, independently from age, sex, performance status and location of the primary tumor.

In a subgroup analysis of patients, who were given first line IFL/bevacizumab followed by oxaliplatin-based progression therapy a median overall survival of 25.1 months was showed, compared to 19.6 months for patients receiving no oxaliplatin therapy. Preliminary data of second line treatment with FOLFOX and bevacizumab showed increased response from 21.8% versus 9.2% in the FOLFOX/placebo group ($p = 0.0001$).

These data suggest that a subset of patients may still benefit from anti-angiogenic treatment in second line therapy, but most patients will have only side-effects.

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. 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, 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.

1.3 Bevacizumab

The monoclonal antibody bevacizumab 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.

Bevacizumab is registered for clinical use in metastatic colon carcinoma. It proved to be also promising (in combination with conventional chemotherapy) in patients with NSCLC and breast cancer.

Study objective

To recognize the distribution pattern of ¹¹¹In-bevacizumab in patients who show response on treatment with bevacizumab. The ultimate goal is to identify and select patients who can be successfully treated.

Study design

Observational study evaluating the feasibility of ¹¹¹In-bevacizumab in patients who show response on bevacizumab therapy.

Distribution kinetics of ¹¹¹In-bevacizumab will be evaluated in responding patients (see patients and methods) receiving first line chemotherapy.

The following procedure will be followed:

- At day 14 of the first chemotherapy cycle (following inclusion in the study protocol) patients will be injected with ¹¹¹In-bevacizumab.
- Gammacamera imaging will initially be performed at day 0, 2, 4 and 7 days after a single intravenous administration of 150 MBq ¹¹¹In-bevacizumab (± 10 mg protein). (The optimal time to scan the patients will be determined after two or three patients. Hereafter patients will only be scanned once or twice after tracer injection, most likely on day 0 and 4 after tracer injection.)

Planar whole body imaging will be performed, using a two-headed gammacamera, equipped with parallel-hole medium-energy collimators, at a scan speed of 10 cm/min (day 0 and 2 after injection) or 5 cm/min (day 4 and 7 after injection) and stored digitally in a 256 x 1024 matrix. An aliquot of dose will be scanned simultaneously. Optionally, single photon emission computed tomography (SPECT) will be performed of regions. Per imaging session, the total amount of scan time will not exceed 90 minutes.

50 ml of blood will be drawn before administration of ¹¹¹In-bevacizumab and

before every scan to determine the anti-angiogenic response in the circulation and levels of ¹¹¹In-bevacizumab in the circulation. (see paragraph 6.3).

Study burden and risks

In this study ¹¹¹In-bevacizumab is administered in tracer-dose, therefore the risk of pharmacological side-effects is minimized. Although the additional risk of administration of a bevacizumab tracer dose (± 10 mg) beside first line chemotherapy including bevacizumab therapy (250-400 mg/every 2 weeks) is most likely negligible, it can not be completely excluded.

The most common side-effects reported after first line chemotherapy with bevacizumab therapy are leukopenia, diarrhea, hypertension, thrombotic events, deep thrombophlebitis, 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 tracer dose of ¹¹¹In-bevacizumab can induce any adverse effect is unknown. Although no toxicity is expected from the tracer-dose, if present, toxicity will be scored according to the Common Toxicity Criteria version 3.0.

Administration of ¹¹¹In-bevacizumab entails radiation load for the participating patients. It has been calculated that a dose of 150 MBq will lead to a radiation load of 27mSv (see appendix 13.3). For comparison purposes, a CT-abdomen will lead to a radiation dose of 10-15 mSv. The poor prognosis of this patient group [5 year survival <20%] 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

1. Metastatic colon cancer.
2. Decrease in CEA levels [-25%] after the 1st or 2nd cycle of first line chemotherapy, including bevacizumab, or decrease in size of measurable valuable lesion.
3. At least 18 years of age.
4. A life expectancy of at least 3 months.
5. Adequate hematologic, hepatic, and renal function.
6. Signed written informed consent.
7. Able to comply with the protocol.

Exclusion criteria

1. Prior chemotherapy or biological therapy for metastatic disease.
2. Radiotherapy within 14 days before the start of the study of the involved area.
3. Major surgery within 28 days before the initiation of the study.
4. Clinically significant cardiovascular disease.
5. 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.
6. CNS metastases (CT-scan not mandatory).
7. Treatment with any investigational drug within 30 days before the start of the study.
8. Prior allergic reaction to immunoglobulins or immunoglobulin allergy.

Study design

Design

Study type: Observational invasive

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status: Recruitment stopped

Start date (anticipated): 01-05-2007

Enrollment: 6

Type: Anticipated

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	EUCTR2007-001467-30-NL
CCMO	NL17093.042.07