A phase II/III study of high-dose, intermittent sunitinib in patients with recurrent GBM

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON50728

Source
ToetsingOnline

Brief title
Phase II/III study of high-dose, intermittent sunitinib in recurrent GBM

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym
Glioblastoma multiforme; Brain cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Divisie I Beheer BV

Intervention

Keyword: Glioblastoma multiforme, High-dose sunitinib, recurrent GBM, Targeted therapy

Outcome measures

Primary outcome

The primary objective is to determine the effect of high-dose sunitinib versus standard treatment with lomustine on six-month progression-free survival (PFS6) in patients with recurrent GBM, using the RANO criteria.

Secondary outcome

Secondary objectives are:

1. To determine the effect of high-dose sunitinib on overall survival (OS 9, OS 12) in patients with recurrent GBM.

2. To assess the objective radiological response rate, using the RANO criteria.

3. To assess the safety and toxicity during treatment, using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

4. To assess patient-oriented criteria: steroid use and health-related quality of life (reported by patients and caregivers/relatives).

5. To explore the potential value of blood markers for molecular diagnostics, disease and response monitoring.

6. To explore if MGMT promoter methylation status modulates the response to sunitinib.

Study description

Background summary

Glioblastoma multiforme (GBM), the most common primary brain tumor in adults, universally recurs and inevitably results in death despite optimal first-line treatment. To date, no standard treatment approach for recurrent disease exists for these patients. Therefore, treatment of recurrent glioblastoma continues to represent a clinically unmet need.

In few preclinical and clinical trials tyrosine kinase inhibitors (TKIs) were studied as treatment for GBM. Although preclinical studies with TKIs showed promising results in GBM, no relevant clinical activity was observed at regular doses in conventional schedules.
We recently studied a TKI, sunitinib, at an alternative, intermittent, high-dose regimen and found that it completely blocks tumor growth in vitro and in vivo. Supported by these results, a phase I/II clinical trial with pulsatile, high-dose sunitinib treatment was initiated. After inclusion of more than 80 patients, we conclude that this alternative schedule is safe and has promising antitumor activity in heavily pretreated patients with various solid malignancies.

Encouraged by these findings, we propose to study this alternative, intermittent, high-dose sunitinib treatment strategy in patients with recurrent GBM.

Study objective

The primary objective is to determine the effect of high-dose sunitinib versus standard treatment with lomustine on six-month progression-free survival (PFS6) in patients with recurrent GBM, using the RANO criteria.

Secondary objectives are:
1. To determine the effect of high-dose sunitinib on overall survival (OS 9, OS 12) in patients with recurrent GBM.
2. To assess the objective radiological response rate, using the RANO criteria.
3. To assess the safety and toxicity during treatment, using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.
4. To assess patient-oriented criteria: steroid use and health-related quality of life (reported by patients and caregivers/relatives).
5. To explore the potential value of blood markers for molecular diagnostics, disease and response monitoring.
6. To explore if MGMT promoter methylation status modulates the response to sunitinib.

Study design

Multicenter, open label, phase II/III, randomized clinical trial with high-dose sunitinib versus lomustine (CCNU) in patients with recurrent GBM.

After randomization, 100 patients will be divided equally over two treatment groups and will receive:
• Group 1 (experimental arm): Sunitinib, 700 mg administered orally once every two weeks.
• Group 2 (control arm): Lomustine 110 mg/m2, taken orally on day 1 every 6 weeks.

Disease will be assessed by MRI according to an uniform neuro-oncology protocol every 6 weeks for the first 6 months and every 12 weeks until documented progression. Safety profile of both treatment strategies will be assessed separately for each cycle of therapy and every 12 weeks after the end of treatment if adverse effects have not resolved or are newly emerging. Furthermore, quality of life assessment takes place every 6 weeks using questionnaires.

Intervention

Patients in the experimental arm will receive sunitinib, 700 mg administered orally once every two weeks. Patients in the control arm will receive lomustine, 110 mg/m2 (capped at 200 mg), taken orally on day 1 every 6 weeks.

Study burden and risks

The most common (>= 20%) adverse reactions of sunitinib treatment are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia, and bleeding.

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. Signed (by the patient or legally acceptable representative) and dated Informed Consent Form
2. Histologically confirmed primary or secondary glioblastoma with unequivocal first progression, at least 3 months off radiotherapy.
3. No more than one line of chemotherapy (concurrent and adjuvant temozolomide based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). Chemotherapy must have been completed at least 4 weeks prior to randomization.
4. Patients may have undergone surgery for recurrence. If operated, residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence.
5. No radiotherapy, stereotactic radiosurgery or brachytherapy as treatment for recurrence.
6. Patients must have a Karnofsky Performance Score >= 70%
7. Patients need to have adequate hematological, renal and hepatic function as assessed by the following laboratory requirements to be conducted within seven days prior to start study treatment:
a. Hemoglobin >= 7.0 mmol/L
b. Absolute neutrophil count (ANC) >= 1.5 x 109/L
c. Platelet count >= 100 x 109/L
d. ALAT and ASAT <= 2.5 x ULN
e. Serum creatinine eGFR >= 50 ml/min
f. Albumin >= 25 g/L
8. Age >= 18 years
9. Male and female patients with reproductive potential must use an approved contraceptive method during and for three months after discontinuation of study treatment.
10. Patients must be able to swallow oral medication.

Exclusion criteria

1. Evidence of a significant uncontrolled concomitant disease, such as cardiovascular disease (including stroke, New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to screening, unstable arrhythmia, clinically significant valvular heart disease and unstable angina); nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture.
2. Patients with a prior (< 5 years) or concomitant second malignancy.
3. Prior radiotherapy in the abdomen or in the lungs or in more than 3 vertebrae in the spine (Less than 3 vertebrae are considered a small radiation field and eligibility will be decided on an individual basis from the PI)
4. Poorly controlled hypertension despite adequate blood pressure medication. Blood pressure must be <= 160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 2 separate measurements.
5. Known active bacterial, viral, fungal, mycobacterial, or other infection (including HIV and atypical mycobacterial disease, but excluding fungal infection of the nail beds.)
6. Initial MR-scan of the brain showing intratumoral hemorrhage, except for stable post-operative grade 1 hemorrhage.
7. Known hypersensitivity to sunitinib or to its excipients.
8. Presence of any significant central nervous system or psychiatric disorder(s) that would interfere with the patient*s compliance.
9. Use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic (as opposed to prophylactic) purposes.
10. Use of strong hepatic enzyme-inducing antiepileptic drugs, such as carbamazepine, phenobarbital and phenytoin. If a patient uses one or more of these specific antiepileptic drugs, the must switch to an antiepileptic drug that does not interact with cytochrome P450 (CYP450) liver enzymes, such as levetiracetam, prior to the start of study treatment.
11. Drug or alcohol abuse.
12. Females who are pregnant or breast-feeding.
13. Any evidence of a disease or condition that might affect compliance with the protocol or interpretation of the study results or render the patient at high risk from treatment complications.
14. Unwillingness or inability to comply with study and follow-up procedures.
15. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2018
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Belustine
Generic name:	Lomustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sutent
Generic name:	Sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	07-07-2016
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-001797-15-NL
CCMO	NL57648.029.16