A phase I trial for the addition of chloroquine, an autophagy inhibitor, to concurrent chemoradiation for newly diagnosed glioblastoma

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Primary objective• To determine the MTD/RPTD for CQ in combination with concurrent radiotherapy with daily TMZ in patients with a newly diagnosed GBM.Secondary objectives• To characterize the safety and tolerability of CQ in combination with...

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

Summary

ID

NL-OMON44953

Source
ToetsingOnline

Brief title
Chloroquine for the treatment of glioblastoma

Condition

- Nervous system neoplasms malignant and unspecified NEC
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Synonym
astrocytoma grade IV, Glioblastoma, malignant braintumour

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Chloroquine, Glioblastoma, Radiotherapy, Temozolomide

Outcome measures

Primary outcome

• Incidence of dose-limiting toxicities.

Secondary outcome

• Adverse Events (AEs), serious AEs (SAEs), changes in haematology and chemistry values, electrocardiograms, tone audiograms or ophthalmologic examination.

• Pharmacokinetics of CQ

• Presence of autophagic marker (LC3b)

• Gene mutation, deletion or amplification such as MGMT, EGFRvIII in tumor tissue pre-treatment

• Radiological response on follow-up MRI

• Time from inclusion until death from any cause

• Time from inclusion until disease progression or death

Study description

Background summary

Patients with a glioblastoma (GBM) have a poor prognosis with a median survival of 14.6 months after maximal treatment with a resection and chemoradiation. Since the pivotal trial evaluating the effect of temozolomide (TMZ), overall

survival has not increased.
Treatment of GBM xenografts in vivo with chloroquine (CQ), an antimalarial agent, has been shown to reduce the hypoxic fraction and sensitizes tumors to radiation. Epidermal growth factor receptor (EGFR) amplification or mutation is regularly observed in GBM and is thought to be a major contributor to radioresistance. The most common EGFR mutation in GBM (EGFRvIII) is present in 50-60% of patients whose tumor shows amplification of EGFR. EGFR provides cells with a survival advantage through autophagy when exposed to stresses such as hypoxia and nutrient starvation. This effect is even more pronounced in EGFRvIII overexpressing tumors. Previously, the potential effect CQ has been demonstrated in a small randomized controlled trial in GBM treated with radiotherapy and carmustine, which showed a trend towards increased overall survival. This effect was even more pronounced in EGFRvIII positive tumors. However, as the intracellular effects of CQ are dose-dependent the maximum tolerated dose for CQ in combination with concurrent radiotherapy with daily TMZ needs to be established.

Study objective

Primary objective
• To determine the MTD/RPTD for CQ in combination with concurrent radiotherapy with daily TMZ in patients with a newly diagnosed GBM.
Secondary objectives
• To characterize the safety and tolerability of CQ in combination with concurrent radiotherapy with daily TMZ.
• To describe the pharmacokinetic profile of CQ in combination with concurrent radiotherapy with daily TMZ.
• To describe the pharmacokinetic profile of CQ in relation to toxicity and the mean change in LC3b.
• To describe the mean change in LC3b in relation to EGFR genotype and toxicity.
• To describe the radiological response of the tumor after treatment with CQ in combination with concurrent radiotherapy with daily TMZ.
• To describe clinical outcome

Study design

Open label, multi center combination phase I trial.

Intervention

Eligible patients will receive radiotherapy and chemotherapy according to standard protocol for newly diagnosed GBM. This consists of 33 daily fractions of 1.8 Gy to the tumor and surrounding margin in combination with TMZ 75 mg/m² po qd and six adjuvant cycles of TMZ 150 - 200 mg/m² po qd.

Treatment will be combined with daily intake of escalating doses of CQ. CQ will

start with week before the start of radiotherapy and end on the last day of radiotherapy. Three cohorts of 3 patients will be treated with different doses of CQ. The three predetermined dose levels are 200mg, 400mg and 600mg. Three additional patients will be added to a cohort in case of dose limiting toxicity. In case of dose limiting toxicity, a lower dose level (-100mg) may be considered. After establishing the maximum tolerated dose, 3 patients will be added to this dose level to confirm safety. This results in a maximum of 9 patients at this dose level.

Study burden and risks

Chloroquine has a known mild toxicity profile and can be administered orally. Theoretically blocking autophagy can also occur in normal cells despite the pre-clinical evidence to the contrary. This could lead to enhanced toxicity of radiotherapy and TMZ. The combination of CQ and TMZ may lead to an increased rate of haematological toxicity for which TMZ needs to be (temporarily) discontinued. Radiosensitisation of the skin after cranial irradiation has been sporadically described.
Inhibition of autophagy with CQ may inhibit the anti-tumor immune response.

Subjects are required to pay extra visits to the hospital in order to perform extra tests in order to identify toxicity. These tests include ophthalmologic examinations, ECGs and tone audiograms. Furthermore, subjects will receive standard blood tests during treatment. At this time, additional blood tubes will be drawn in order to investigate the pharmacokinetics of CQ, the mean change in LC3b and the effect of treatment on the anti-tumor immune response in the phase I study.

Contacts

Public
MAASTRO clinic

Dr. Tanslaan 12 Dr. Tanslaan 12
Maastricht 6229 ET
NL
Scientific
MAASTRO clinic

Dr. Tanslaan 12 Dr. Tanslaan 12
Maastricht 6229 ET
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Histologically confirmed grade IV supratentorial astrocytoma (glioblastoma multiforme)
• Tumor tissue available for histopathological analysis (MGMT, EGFRvIII)
• Diagnosis must have been made by biopsy or resection <= 6 weeks prior to study entry
• 18 - 70 years
• Karnofsky performance status >=70
• Absolute neutrophil count at least 1.5 x 109/L and platelets at least 100 x109/L
• Adequate renal function: serum creatinine <= 1.5 x upper limit of normal (UNL)
• Adequate hepatic function: total bilirubin <= 1.5 x UNL for the instituion; ALT, AST, and alkaline phosphatase <= 3 x UNL for the institution
• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
• Willingness to use contraception by a method that is deemed effective by the Investigator throughout the treatment period and for at least 30 days following the last dose of therapy
• If female, postmenopausal for at least 2 years, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing an appropriate method of birth control
• If male, subject must be surgically sterile or practicing an appropriate method of contraception and refrain from sperm donation, from initial drug administration until 90 days after the last dose of study drug:
• Ability to swallow and take oral medication.
• Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations

Exclusion criteria

• Prior radiotherapy
• Prior chemotherapy

• Recent (< 3 months) severe cardiac disease (NYHA class >1) (congestive heart failure, infarction)
• History of cardiac arrythmia which is symptomatic and requiring treatment, or asymptomatic sustained ventricular tachycardia. Asymptomatic atrial fibrillation controlled on medication is allowed.
• Cardiac conduction disturbances or medication potentially causing them
• Treatment with investigational drugs in 4 weeks prior to or during this study
• If the subject has clinically significant and uncontrolled major medical condition(s) including but not limited to uncontrolled nausea/vomiting/diarrhea; active uncontrolled infection; psychiatric illness/social situation that would limit compliance with study requirements; any medical condition, with the opinion of the study investigator, places the subject at an unacceptably high risk for toxicities
• Another active malignancy within the past 3 years except for any cancer in situ that the principal investigator considers to be cured
• Chronic systemic immune therapy (with the exception of corticosteroids)
• Concurrent cytochrome P450 enzyme-inducing anticonvulsant drugs
• Known Glucose-6-phosphate dehydrogenase (G6PD) deficiency
• Psoriasis or porphyria
• Known hypersensitivity to 4-aminoquinoline compound
• Retinal or visual field changes unrelated to the tumor location prior to 4-aminoquinoline compound use

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):	06-09-2016
Enrollment:	18
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	27-05-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-06-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2015-002082-38-NL
ClinicalTrials.gov	NCT02378532
CCMO	NL52723.068.15

Study results

Date completed:	30-07-2019
Actual enrolment:	13