International Multicenter Phase I trial of Hydroxyurea in Combination with Dose-Intense Temozolomide in Recurrent Glioblastoma.

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This is a phase I study of hydroxyurea and dose-intense temozolomide in patients with recurrent glioblastoma that are elegise for re-challenge temozolomide.Primary Objective: To determine the maximal tolerated dose and safety profile of daily…

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

Summary

ID

NL-OMON50467

Source
ToetsingOnline

Brief title
HUTMZ

Condition

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

Synonym
brain tumor, High grade glioma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Janivo Stichting

Intervention

Keyword: brain tumor, Hydroxyurea, recurrent glioblastoma, Temozolomide

Outcome measures

Primary outcome

Primary Objective:

To determine the maximimum tolerated dose (MTD) and safety profile of daily hydroxyurea in combination with continuous dose-intense temozolomide (50 mg/m2/day) in patients with recurrent GBM. If 1 of 3 patients develops DLT during the first 8 weeks of treatment that Dose Cohort will be expanded by 3 additional patients at the same dose level. The 3 additional patients must be followed for at least 8 weeks and toxicity must be evaluated before continuing escalation. If no additional DLT are observed (i.e. 1/6 DLT total in the expanded Dose Cohort) then 3 new patients may be entered at the next highest dose level. However, if 1/3 patients experience DLT in this expanded cohort (i.e. 2/6 DLT total in the expanded Dose Cohort) then this will be declared the MTD. If 2/3 or 3/6 patients experience DLT at any dose level (above dose level -1) then the next cohort of 3 patients will be treated at a dose one level lower than the dose at which 2/3 DLT were observed. All of the above holds for DLT attributed to hydroxyurea. The dose of hydroxyurea in combination with temozolomide will not be escalated above 2000 mg QD, the maximum daily dose

when used in monotherapy for other malignancies such as resistant chronic myelocytic leukemia.

Secondary outcome

Secondary Objectives:

• To estimate the preliminary median progression-free survival of patients with recurrent glioblastoma treated with daily hydroxyurea in combination with dose-intense temozolomide.

• To estimate the preliminary radiographic response proportion in patients with measurable disease.

• To estimate the preliminary median overall survival.

• Exploratory correlation of treatment outcomes (progression-free and overall survival with MGMT promoter methylation status in archival tumor specimens.

Study description

Background summary

More than half of the 19,000 patients in the U.S. and the Netherlands diagnosed with malignant primary brain tumors each year have glioblastoma (GBM), the most common primary malignant brain tumor in adults. Glioblastoma is a uniformly fatal disease with an average survival of less than one year, and even aggressive treatment with surgery, radiation and/or chemotherapy fails to extend the life span of patients by more than a few months. Primary treatment for patients with GBM includes surgical resection. Temozolomide has been approved for treatment of patients with GBM and is used both in recurrent GBM

as well as in combination with radiotherapy following surgery resulting in an improvement of survival. However, improvements in median progression-free survival (PFS) and overall survival (OS) were modest for newly diagnosed GBM patients (6.9 and 14.6 months, respectively), and all patients ultimately fail. Following recurrence, there is no identified therapy that has demonstrated clinical benefit such as improved survival in these patients. Because the prognosis for such patients is grave, many patients receive experimental biotherapy or chemotherapy in the setting of clinical trials. However, in large, pooled databases patients with recurrent GBM treated with various experimental approaches, only 9-15% were alive and without disease progression at 6 months. There remains a major unmet need for new treatment options in glioblastoma.

Hydroxyurea has been previously evaluated in malignant gliomas in combination with radiation or cytotoxic chemotherapy and has shown limited efficacy. However, hydroxyurea was not evaluated with an agent with validated efficacy in glioblastoma such as temozolomide. As a single agent, imatinib did not demonstrate efficacy in phase II trials of recurrent GBM. However, more recently, moderate improvements in progression-free survival compared to historical controls have been observed in small series of recurrent glioblastoma patients with the combination of daily hydroxyurea and imatinib, a small molecule selective receptor tyrosine kinase inhibitor of the Bcr- Abl, c-KIT, c-fms, and platelet-derived growth factor receptor (PDGFR) kinases. Hydroxyurea penetrates the blood-brain barrier, and enhanced drug delivery imatinib into the CNS was postulated as a possible reason for the efficacy seen with this combination.

Dr. Tannous performed an in vitro drug screening to identify compounds that would overcome resistance to temozolomide using standard glioblastoma cell lines. In his studies, hydroxyurea potently sensitized temozolomide-resistant GBM cells to rechallenge with temozolomide in vitro. GBM cells were cultured in temozolomide until a resistant clone emerged. When combined with hydroxyurea, temozolomide rechallenge resulted in potent cytotoxicity in vitro.

In addition, temozolomide resistant GBM cells were implanted orthotopically in mouse brains, and the combination of temozolomide and hydroxyurea resulted in significant improvement in animal survival. These data were then confirmed using GBM cells obtained from patient tissue sections from newly diagnosed tumors with methylated and unmethylated MGMT promoter as well as from recurrent tumors.

In the animal survival studies, the combination of hydroxyurea and temozolomide regimen was determined empirically, and the dose of each drug was based on prior reports using each as a single agent. Hydroxyurea was dosed orally 50mg/kg 4 days/week and temozolomide was dosed 10mg/kg 4 days/week. This combination was well tolerated with no apparent serious toxicity.

The combination dose regimen and schedule proposed in this study was generated with the goal of recapitulating the combination regimen used in our animal survival study which demonstrated efficacy of this combination against temozolomide-resistant tumors. The dosing in the animal study was daily for 4 of 7 days. Among the various dose-intense temozolomide schedules, we selected the continuous dose-intense temozolomide regimen (50 mg/m2/day) based on reports of modest efficacy in recurrent GBM patients who had been previously treated with different schedules of temozolomide and the relatively mild myelosuppressive effect of this schedule. This schedule may allow for concomitant daily dosing with hydroxyurea, which would closely recapitulate the regimen in our animal studies.

Study objective

This is a phase I study of hydroxyurea and dose-intense temozolomide in patients with recurrent glioblastoma that are elegise for re-challenge temozolomide.

Primary Objective: To determine the maximal tolerated dose and safety profile of daily hydroxyurea in combination with dose-intense temozolomide (50 mg/m2/day) in patients with recurrent glioblastoma.

Secondary Objectives:
1. To estimate the preliminary median progression-free survival of patients with recurrent glioblastoma treated with daily hydroxyurea in combination with dose-intense temozolomide.
2. To estimate the preliminary radiographic response proportion in patients with measurable disease.
3. To estimate the preliminary median overall survival.
4. Exploratory correlation of treatment outcomes (progression-free and overall survival with MGMT promoter methylation status in archival tumor specimens.

Study design

All patients must have had histological confirmation of glioblastoma by either biopsy or resection. Patients with progressive disease by standard imaging criteria or by tissue biopsy will be eligible. Patients must not have had prior anti-vascular endothelial growth factor (VEGF) therapy as this therapy interferes with the interpretation of MRI-imaging. After registration, oral hydroxyurea (dose specified by the Dose Cohort) and oral temozolomide (50 mg/m2/day) will be administered daily in 28-day cycles for 12 cycles or until unacceptable toxicity, intolerance, progressive disease or withdrawal of consent. Patients will be treated in dose cohorts of 3 with each cohort receiving a specific daily dose assignment of hydroxyurea. All patients in the study will receive temozolomide at 50 mg/m2/day (*dose-intense* schedule). The dose levels will be increased in a conventional 3+3 design.

Hydroxyurea and temozolomide will be administered every 4 weeks, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Oral hydroxyurea (dose specified by the Dose Cohort below) and oral temozolomide (50 mg/m2/day) will be administered daily in 28-day cycles for 12 cycles or until unacceptable toxicity, intolerance, progressive disease, or withdrawal of consent. Patients will be treated in dose cohorts of 3 with each cohort receiving a specific daily dose assignment of hydroxyurea.

All patients in the study will receive temozolomide at 50 mg/m2/day (*dose-intense* schedule). The starting dose level for hydroxyurea will be 200 mg daily (QD).

The dose will be escalated in cohorts of at least 3 patients according to the escalation scheme starting at Dose Cohort 1. All three patients at each dose level must be followed for at least 4 weeks before any new patients may be entered at the next dose level. Escalation to the next dose level will occur if no dose-limiting toxicity (DLT) is observed. If 1 of 3 patients develops DLT during the first 4 weeks of treatment that Dose Cohort will be expanded by 3 additional patients at the same dose level. The 3 additional patients must be followed for at least 4 weeks and toxicity must be evaluated before continuing escalation. If no additional DLT are observed (i.e. 1/6 DLT total in the expanded Dose Cohort) then 3 new patients may be entered at the next highest dose level. However, if 1/3 patients experience DLT in this expanded cohort (i.e. 2/6 DLT total in the expanded Dose Cohort) then this will be declared the MTD. If 2/3 or 3/6 patients experience DLT at any dose level (above dose level -1) then the next cohort of 3 patients will be treated at a dose one level lower than the dose at which 2/3 DLT were observed. All of the above holds for DLT attributed to hydroxyurea. The dose of hydroxyurea in combination with temozolomide will not be escalated above 2000 mg QD, the maximum daily dose when used in monotherapy for other malignancies such as resistant chronic myelocytic leukemia. We anticipate enrollment of 15-30 patients in this study.

The MTD of hydroxyurea when used in combination with dose-intense temozolomide identified in this study will be the recommended dose for future phase II studies.

Intervention

Hydroxyurea and temozolomide will be administered every 4 weeks, with 28 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Oral hydroxyurea (dose specified by the Dose Cohort below) and oral temozolomide (50 mg/m2/day) will be administered daily in 28-day cycles for 12 cycles or until unacceptable toxicity, intolerance, progressive disease, or withdrawal of consent. Patients will be treated in dose cohorts of 3 with each cohort receiving a specific daily dose assignment of hydroxyurea.

All patients in the study will receive temozolomide at 50 mg/m2/day (*dose-intense* schedule). The starting dose level for hydroxyurea will be 200 mg daily (QD). The dose levels will be increased in a conventional 3+3 design as follows:

Dose Escalation Schedule

Dose Cohort Hydroxyurea Dose Temozolomide Dose
-1 200 mg, every other day (QOD) 50 mg/m2/day
0 - Starting Dose 200 mg, daily (QD) 50 mg/m2/day
1 400 mg, QD 50 mg/m2/day
2 600 mg, QD 50 mg/m2/day
3 800 mg, QD 50 mg/m2/day
4 1000 mg, QD 50 mg/m2/day
5 1200 mg, QD 50 mg/m2/day
6 1500 mg, QD 50 mg/m2/day
7 1700 mg, QD 50 mg/m2/day
8 2000 mg, QD 50 mg/m2/day

The dose will be escalated in cohorts of at least 3 patients according to the escalation scheme above starting at Dose Cohort 1. All three patients at each dose level must be followed for at least 8 weeks before any new patients may be entered at the next dose level. Escalation to the next dose level will occur if no dose-limiting toxicity (DLT) is observed (see Section 5.4 for definition of dose-limiting toxicity). If 1 of 3 patients develops DLT during the first 8 weeks of treatment that Dose Cohort will be expanded by 3 additional patients at the same dose level. The 3 additional patients must be followed for at least 8 weeks and toxicity must be evaluated before continuing escalation. If no additional DLT are observed (i.e. 1/6 DLT total in the expanded Dose Cohort) then 3 new patients may be entered at the next highest dose level. However, if 1/3 patients experience DLT in this expanded cohort (i.e. 2/6 DLT total in the expanded Dose Cohort) then this will be declared the MTD. If 2/3 or 3/6 patients experience DLT at any dose level (above dose level -1) then the next cohort of 3 patients will be treated at a dose one level lower than the dose at which 2/3 DLT were observed. All of the above holds for DLT attributed to hydroxyurea. The dose of hydroxyurea in combination with temozolomide will not be escalated above 2000 mg QD, the maximum daily dose when used in monotherapy for other malignancies such as resistant chronic myelocytic leukemia.

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The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end

of each course.

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

• Disease progression

• Intercurrent illness that prevents further administration of treatment

• Unacceptable adverse event(s)

• Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

• Participant decides to withdraw from the study

• General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Duration of Follow Up

Following discontinuation of treatment, participants will be followed for two years for survival and for progression or until death, whichever occurs first. Follow-up data will be collected as feasible either by follow-up visits, or telephone contact to the subject*s outside physician monthly for the first 2 months and then every 2 months to assess tumor status. Participants removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

For participants who continue to be followed by the Investigator and who have no evidence of progression at the time of treatment discontinuation, repeat tumor assessments approximately every 8 weeks is suggested in the appropriate setting.

For participants who are followed by providers other than the Investigator, follow-up for survival is suggested by telephone contact or other means to obtain timely regular follow-up data. Follow-up should be monthly for the first 2 months and then every 2 months thereafter.

Participants will be removed from the study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the participant was removed must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form should be filled out when a participant completes study treatment and again when the participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

DOSING DELAYS/DOSE MODIFICATIONS

ANC, platelet count, total white blood cell count, and hemoglobin must be grade 1 or greater prior to the start of each cycle.

In the event of Grade 3 or 4 hematological toxicity (neutropenia, thrombocytopenia, or anemia), both temozolomide and hydroxyurea must be held until these counts recover to at least Grade 1. Study drugs may be held for up to 28 days. Once counts have recovered sufficiently to restart therapy, the dose of hydroxyurea should be decreased 2 dose levels (see Hydroxyurea Dose Levels above and Hydroxyurea Dose Reduction Table below for guidance) and the dose of temozolomide should be continued at the prior dose.

If after 2 successive dose reductions of hydroxyurea the Hydroxyurea Dose Reduction Table below specifies discontinuation of therapy, then the patient will be taken off of study for unacceptable toxicity.

If after 2 successive dose reductions of hydroxyurea the participant is eligible for a 3rd hydroxyurea dose reduction based on the Hydroxyurea Dose Reduction Table below, the patient will also reduce one Dose Level of temozolomide.

If the participant requires discontinuation of temozolomide (reached Temozolomide Dose Level -2), the participant will be taken off study for unacceptable toxicity.

Dose delays and modifications:

Dose Level Hydroxyurea Dose
-2 Discontinue
-1 200 mg, every other day (QOD)
0 200 mg, daily (QD)
+1 400 mg QD
+2 600 mg QD
+3 800 mg, QD
+4 1000 mg, QD
+5 1200 mg, QD
+6 1500 mg, QD
+7 1700 mg, QD
+8 2000 mg, QD

Dose Level Temozolomide Dose
-2 Discontinue
-1 25 mg/m2/day
0 50 mg/m2/day

Study burden and risks

Not applicable

Contacts

Public
Vrije Universiteit Medisch Centrum

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Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Histologically or cytologically confirmed glioblastoma multiforme

Patients may have had any number of prior therapies for glioblastoma.
Patients must be at least 28 days from any investigational agent, 28 days from prior cytotoxic therapy (except 23 days from prior temozolomide, 14 days from vincristine, 42 days from nitrosoureas, 21 days from procarbazine administration), and 7 days for patients who received metronomic chemotherapy or non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc.
Age >=18 years en mentally competent
Karnofsky Performance Status (KPS) >=60%
Participants must have normal organ and marrow function as defined below (leukocytes >=3,000/mcL, absolute neutrophil count >=1,500/mcL, platelets >=100,000/mcL, total bilirubin within normal institutional limits, AST(SGOT)/ALT(SGPT) <=2.5 × institutional upper limit of normal, creatinine below upper limit of normal institutional limits OR creatinine clearance >=60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal)
Progressive disease on contrast-enhanced brain CT or MRI as defined by RANO

Exclusion criteria

Participants who are receiving any other investigational agents or devices in investigation for glioblastoma.
No previous treatment with an anti-VEGF inhibitor.
History of allergic reactions attributed to compounds of similar chemical composition to temozolomide and/or hydroxyurea.
Uncontrolled intercurrent illness including, that would limit compliance with study requirements.
Pregnant women
HIV-positive participants on combination antiretroviral therapy
Patients with a history of a different malignancy are ineligible except for the following circumstances: if they have been disease-free for at least 3 years and are deemed by the investigator to be at low risk for recurrence of that malignancy; patients with treated cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin. Patients will not be eligible if they have evidence of other malignancy requiring therapy other than surgery within the last 3 years.
Major surgery within 2 weeks of start of study drug; or not fully recovered from any side effects of previous procedures.
Presence of extra-cranial metastatic disease.

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):	08-03-2018
Enrollment:	49
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydroxycarbamide medac
Generic name:	Hydroxyurea
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temodar
Generic name:	Temozolomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2020
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	EUCTR2016-001558-17-NL
CCMO	NL55783.029.16