International study in multiple centers studying the effect of hydroxy-urea and temozolomide chemotherapy in patients with a recurrent malignant brain tumor (Glioblastoma)

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20720

Source
NTR

Brief title
HUTMZ

Health condition

Brain tumor, glioma, glioblastoma, recurrent glioblastoma, glioblastoma multiforme

Hersentumor, glioom, glioblastoom, recidief glioblastoom, glioblastoma multiforme

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: Janivo Stichting
CCA fonds

Intervention

Outcome measures

Primary outcome

To determine the maximimum tolerated dose (MTD) and safety profile of daily hydroxyurea in combination with continuous dose-intense temozolomide in patients with recurrent GBM.

Secondary outcome

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

Glioblastoma is the most frequent and most malignant subtype of primary brain tumors. Unfortunately, over the last two decades, the only major development in the treatment of patients with GBM has been the addition of the DNA alkylating agent TMZ to the standard of care including surgery and radiation resulting in an improvement of the overall survival from 12.1 to 14.6 months
1. More than 90% of patients though die within 5 years of diagnosis. This colossal failure has been partially attributed to development of drug resistance. A major predictor of GBM-response to TMZ is the intrinsic MGMT (O6-methylguanine methyl transferase) promoter methylation status. TMZ induces methylation of guanine at O6-position, a change that causes a futile cycle of attempted DNA repair and results in cell apoptosis. MGMT can remove DNA adducts caused by alkylating agents, resulting in resistance to TMZ. Methylation of the MGMT promotor (occurring in approximately half of GBM) leads to a transcriptional silencing of the MGMT-gene. Patients with MGMT methylated promotors are more likely to benefit from the addition of TMZ2. Given that all GBM eventually acquire resistance to TMZ, studies are underway to unravel the molecular changes that occur during treatment and to characterize the mechanisms of resistant recurrences. Through drug screening, we identified HU to sensitize TMZ-resistant GBM cells to TMZ, both in culture and in primary GBM in vivo intracranial models.
We also explored the effect of mechanism behind the synergistic effect of HU+TMZ. HU acts specifically on the S-phase of the cell cycle by inhibiting the enzyme ribonucleotide reductase (RNR), thereby hindering the reductive conversion of ribonucleotides to deoxyribonucleotides

and thus limiting de novo DNA synthesis. This property makes RNR inhibitors like HU an attractive candidate for cancer therapy. Another advantage for the use of HU in GBM is that it increases the blood brain tumor (BBB) permeability of certain chemotherapeutics and therefore could enhance penetration of TMZ into GBM. The Notch pathway is another suggested target for cancer therapy and Notch inhibitors have been reported to synergize with TMZ in GBM. In preliminary experiments we observed that HU also was able to inhibit Notch signaling. We are currently, trying to unravel the exact mechanism through which HU achieves re-sensitization for TMZ. Through its inhibitory effects on the Notch pathway and RNR and possibly increasing permeability of the BBB to TMZ, HU has effects on multiple levels to sensitize cells to TMZ. Our next step is to investigate the safety and MTD of the combination HU+TMZ in patients with rGBM.

1 R Stupp et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med 2005; 352:987-96;
2 ME Hegi et al. MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. N Engl J Med 2005; 352:997-1003;

3 JR Perry et al. Phase II Trial of Continuous Dose-Intense Temozolomide in Recurrent Malignant Glioma: RESCUE Study. JCO 28;12::2051-7 ;

4 C Hunter et al. A hypermutation phenotype and somatic MSH6 mutations in recurrent human malignant gliomas after alkylator chemotherapy. Cancer Res. 2006;66:3987-91.

Study objective

Determining maximal tolerated dose hydroxy-ureum in combination with dose intense temozolomide in patients with recurrent glioblastoma

Study design

Start 01-06-2016, end 01-06-2020

Intervention

Combine hydroxy-ureum with dose-dense temozolomide in patients with recurrent glioblastoma.

Contacts

Public

[default]

The Netherlands
Scientific

[default]
The Netherlands

Eligibility criteria

Inclusion criteria

1. Participants must have histologically or cytologically confirmed glioblastoma multiforme

2. 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.

3. Age ¡Ý18 years. Because no dosing or adverse event data are currently available on the use of hydroxyurea in combination with temozolomide in participants <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

4. Karnofsky Performance Status (KPS) ¡Ý60%

5. Participants must have normal organ and marrow function as defined below:

− leukocytes ¡Ý3,000/mcL

− absolute neutrophil count ¡Ý1,500/mcL

− platelets ¡Ý100,000/mcL

− total bilirubin within normal institutional limits

− AST(SGOT)/ALT(SGPT) ¡Ü2.5 ¡Á institutional upper limit of normal

− creatinine below upper limit of normal institutional limits
OR

− creatinine clearance ¡Ý60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal.

6. Progressive disease on contrast-enhanced brain CT or MRI as defined by RANO Criteria

[22], or have documented recurrent glioblastoma on diagnostic biopsy. Patients who have been previously treated with bevacizumab therapy that have T2-weighted or FLAIR MRI sequences considered to be progressive disease by the study investigator but have no contrast-enhancing areas of recurrent disease are eligible.

7. Interval of at least 2 weeks from any prior neurosurgical resection (1 week for intracranial biopsy) to start of study drug; and patient must have adequate wound healing.

8. Interval of at least 12 weeks from prior radiotherapy unless there is either: a) histopathologic confirmation of recurrent tumor, or b) new enhancement on MRI outside of the radiation treatment (RT) field.

9. Because cytotoxic agents such as temozolomide and hydroxyurea are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of temozolomide and hydroxyurea administration.

10. Patients must have archival tumor tissue available for molecular analysis and must be willing to consent for this tissue to be analyzed as part of this study. However, if no archival tumor tissue is available, the patient will not be excluded from the study.

11. Ability to understand and the willingness to sign a written informed consent document.

Exclusion criteria

1. Participants who are receiving any other investigational agents or devices in investigation for glioblastoma.

2. Patients must not have been previously treated with an anti-VEGF inhibitor.

3. History of allergic reactions attributed to compounds of similar chemical composition to temozolomide and/or hydroxyurea.

4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5. Pregnant women are excluded from this study because hydroxyurea and temozolomide have known teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with hydroxyurea and temozolomide, breastfeeding should be discontinued if the mother is

treated with hydroxyurea and temozolomide.

6. HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with hydroxyurea. In addition, these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

7. 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.

8. Major surgery (not including minor diagnostic procedures such as lymph node biopsy) within 2 weeks of start of study drug; or not fully recovered from any side effects of previous procedures.

9. Presence of extra-cranial metastatic disease.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2016
Enrollment:	35
Type:	Anticipated

Ethics review

Not applicable
Application type: Not applicable

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
NTR-new	NL5768
NTR-old	NTR6009
Other	: Pro-16/11

Study results