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Radiochemotherapy trial with radiotherapy and temozolomide chemotherapy for children and young adolescents 3 years and older to 18 years of age with primary high grade glioma, pontine glioma or gliomatosis cerebri

Submission date 25/05/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 05/06/2009	**Overall study status** Completed	
Last Edited 01/07/2016	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2007-000128-42

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
EudraCT 2007-000128-42; BfArM 4034262

Study information

Scientific Title
International cooperative phase II trials of the HIT-HGG study group for the treatment of high grade glioma, diffuse intrinsic pontine glioma, and gliomatosis cerebri in children and adolescents 3 years and older up to 18 years

Acronym
HIT-HGG-2007

Study objectives
Based on the experience of the Adult Glioblastoma EORTC trial with oral temozolomide and radiotherapy, a phase II trial with oral temozolomide in parallel to radiotherapy and as subsequent consolidation treatment will be performed. This will be investigated if the resulting 6-month event-free-survival (EFS) will support the initiation of a phase III trial in which long term EFS and the randomised evaluation of the therapeutic efficiency of an immune therapeutic approach in parallel to oral temozolomide consolidation chemotherapy will be successful.

Main general objectives:
1. Is a simultaneous radiochemotherapy with radiotherapy and a 5 - 6 weeks course of oral temozolomide at 75 mg/m^2/d followed by additional 12 cycles of oral temozolomide given as a 5 day course at 150 - 200 mg/m^2/d every 28 days efficacious?
2. EFS and treatment related toxicities for each treatment element will be evaluated in comparison to the results of the previous paediatric HIT-GBM-C and -D trials for treatment of primary high grade glioma, diffuse intrinsic pontine glioma, and gliomatosis cerebri

Primary objectives:
1. Is treatment with temozolomide efficacious? Treatment is considered to be efficacious if the probability for "no event within the first 6 months after diagnosis" is not inferior in comparison with the corresponding 6-months EFS rates of the HIT-GBM-C and D cohort. That means that the probability for "no event within the first 6 months after diagnosis" is not less than or equal to 46% for patients with a pontine tumour and not less than or equal to 53% for patients with a non-pontine tumour. The probability for being event-free 6 months after diagnosis is different for patients with and without a pontine tumour.

Secondary objectives:
1. Do the overall survival (OS) and event-free survival (EFS) of patients of the HIT-HGG-2007 trial differ from the OS/EFS of patients of the historical control groups (HIT-GBM-C and -D)?
2. Does the HIT-HGG-2007 treatment leads to different toxicity rates in comparison to the historical control group (HIT-GBM-C and -D)?
3. Has the methylation of the O6-MGMT (O6-methylguanine-DNA methyltransferase) gene promoter within the primary tumour an influence on the EFS? (similar to reports in adult patients with glioblastoma)
4. Do the following clinical parameters have an influence on EFS or OS?
4.1. Tumour location (ICD-O classification)

4.2. Tumour grading
4.3. Centrally reviewed histology (World Health Organization [WHO] classification)
4.4. Extent of tumour resection (as defined by early post surgical imaging, preferentially magnetic resonance imaging)
4.5. Genetic syndromes
4.6. Secondary malignancies
4.7. Age at diagnosis
4.8. Gender
4.9. Relapse treatment
5. Is there an association between these clinical parameters and the affiliation to one of the two patient groups HIT-HGG-2007 and HIT-GBM-C/-D?

Tertiary objectives:
1. Neuropsychological testing and evaluation of the quality of life during different time points in the course of disease and treatment. By establishing this testing program future treatment modalities can be directly compared in regards to neuropsychological outcome and resulting quality of life.
2. Establishment of routine sterile fresh frozen tumour sampling and mailing on dry ice to the tumour tissue bank of the HIT network at the Institute of Neuropathology, Bonn, Germany. Is there an increase of the current tumour bank entry rate which was approximately 15 % of all possible cases within HIT-GBM-D?
3. Establishment of routine investigation of tumour paraffin material for potential therapeutic targets for individualised relapse treatment. These targets include: epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor alpha (PDGFR alpha), c-kit, PTEN, vascular endothelial growth factor receptor (VEGFR) 1,2. Investigations will be performed during central neuropathological review.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Board of the Medical Faculty of the Martin Luther University of Halle-Wittenberg approved on the 19th March 2009

Study design
Multinational prospective non-randomised phase II trial

Primary study design
Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Primary high grade glioma, pontine glioma or gliomatosis cerebri

Interventions
1. Surgery with best possible extent of tumour resection
2. Induction with simultaneous radiochemotherapy:
2.1. Fractionated, locoregional radiotherapy, total dose 54 - 60 Gy
2.2. Simultaneous chemotherapy with oral temozolomide, 7 days per week at 75 mg/m^2/d, starting at day 1 for the entire period of radiotherapy (at maximum 49 days)
3. Consolidation chemotherapy: four weeks after simultaneous radiochemotherapy initiation of a 5 day-course of oral temozolomide [150 - 200 mg/m^2/d], repeated every 28 days for in total 12 courses

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Temozolomide

Primary outcome measure
Event-status 6 months after diagnosis: event/no event (i.e. by magnetic resonance imaging). An "event" is defined as:
1. Progression/relapse of disease
2. Diagnosis of a secondary malignancy
3. Death of any cause

Secondary outcome measures
1. Event-free survival defined as time from diagnosis until the first event, measured after 1 year and 2 years
2. Overall survival defined as time from diagnosis until death of any cause, measured after 6 months, 1 year, and 2 years
3. Common Toxicity Criteria (CTC) toxicity levels of treatment elements

A follow-up of 2 years after study entry is required, however, a long term follow-up is highly recommended. Thus, event-free survival and overall survival will possibly be evaulated after 5 years and longer.

Overall study start date
01/06/2009

Completion date
31/12/2017

Eligibility

Key inclusion criteria
1. Newly diagnosed, previously untreated high grade glioma with central neuropathological review including glioblastoma multiforme (WHO IV), anaplastic astrocytoma (WHO III), anaplastic oligodendroglioma (WHO III), anaplastic mixed glioma/anaplastic oligoastrocytoma (WHO III), anaplastic pilocytic astrocytoma (WHO III), anaplastic ganglioglioma (WHO III), anaplastic pleomorphic xanthoastrocytoma (WHO III), giant cell glioblastoma (WHO IV), and gliosarcoma (WHO IV)
2. Newly diagnosed, previously untreated diffuse intrinsic pontine glioma of all tumour grades with central neuroradiological review
3. Newly diagnosed, previously untreated gliomatosis cerebri of all tumour grades with central neuropathological review
4. Patient aged 3 years and older but under 18 years at time of diagnosis, either sex
5. Written informed consent of the patient and/or the patient's parents or legal guardian according to national laws

Participant type(s)
Patient

Age group
Child

Lower age limit
3 Years

Upper age limit
18 Years

Sex
Both

Target number of participants
135

Key exclusion criteria
1. Pre-treatment of glioblastoma multiforme (WHO IV), anaplastic astrocytoma (WHO III), anaplastic oligodendroglioma (WHO III), anaplastic mixed glioma/anaplastic oligoastrocytoma (WHO III), anaplastic pilocytic astrocytoma (WHO III), anaplastic ganglioglioma (WHO III), anaplastic pleomorphic xanthoastrocytoma (WHO III), giant cell glioblastoma (WHO IV), gliosarcoma (WHO IV), diffuse intrinsic pontine glioma and gliomatosis cerebri differing from study protocol
2. Known hypersensitivity or contraindication to study drugs and/or dacarbazine
3. Prior chemotherapy or radiotherapy which prevents adequate performance of radiotherapy as outlined by the present protocol. This may mainly apply to patients with secondary malignant glioma after previous malignant brain tumour, e.g. medulloblastoma, supratentorial PNET. If previous treatment does not prevent the adequate performance of the outlined treatment protocol patients with secondary malignant glioma will be eligible for the present trial.
4. Other (simultaneous) malignancies
5. Pregnancy and/or lactation
6. Patients who are sexually active refusing to use effective contraception (oral contraception, intrauterine devices, barrier method of contraception in conjunction with spermicidal jelly or surgical sterile)

7. Current or recent (within 30 days prior to start of trial treatment) treatment with another investigational drug or participation in another investigational trial
8. Very poor clinical condition as defined by demand of mechanical ventilation and/or demand for intravenous catecholamines and/or very severe neurological damage equivalent to a coma and/or tetraplegia with complete incapability for communication (deafness, blindness, mutism)
9. Severe concomitant diseases (e.g. immune deficiency syndrome)
10. Known human immunodeficiency virus (HIV) positivity

Country-specifically very young patients may be excluded to comply with national laws or formal insurance requirements.

Date of first enrolment
10/06/2009

Date of final enrolment
31/12/2015

Locations

Countries of recruitment
Austria

Germany

Switzerland

Study participating centre
University Children's Hospital
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Sponsor information

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University/education

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ROR
https://ror.org/05gqaka33

Funder(s)

Funder type
Charity

Funder Name
The German Children's Cancer Foundation (Deutsche Kinderkrebsstiftung) (Germany) (ref: DKS 2009.06)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration