A comprehensive and targeted therapy approach in pediatric malignant pontine gliomas

Published: 14-09-2010
Last updated: 01-05-2024

Phase A:Primary objective: Determining the feasibility of gemcitabine as a radiosensitizer in DIPG Secondary objective: Evaluation of efficacy in terms of clinical and radiological response rate and progression free survivalTertiary objectives:...

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

Summary

ID

NL-OMON44907

Source
ToetsingOnline

Brief title
DIPG study VUmc 01

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain stem glioma, malignant pontine glioma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Stichting Semmy

Intervention

Keyword: Brainstem, Children, Glioma, Pontine

Outcome measures

Primary outcome

Phase A: Tolerability of gemcitabine at 3 dose levels (toxicity according to CTCAE-4)

Phase B: Tolerability of erlotinib and everolimus at two dose levels when added to bevacizumab-irinotecan (toxicity according to CTCAE-4)

Secondary outcome

Phase A:

Secondary endpoint: Clinical reponse rate, response rate on MRI according to the WHO-criteria and the median progression free survival

Tertiary endpoints:

- Quality of life, measured by standardised questionnaires (PedsQl).

- The contribution of MRS to MRI in terms of predictors of survival or disease progression

Phase B:

Secondary endpoint: Survival duration from time of disease progression

Tertiary endpoints:

- Response on MRI according to the WHO criteria

- Quality of life, measured by standardised questionnaires (PedsQl).

- Pharmacokinetics of erlotinib and everolimus

- The contribution of MRS to MRI in terms of predictors of survival/disease

progression

Study description

Background summary

Children with malignant pediatric pontine gliomas have a dismal prognosis. The median overall survival is approximately nine months, the two-year survival less than 10%. In the past twenty years prognosis has remained unchanged, despite several treatment strategies that have been applied. In this study, the feasibility and efficacy of the radiosensitizer gemcitabine and a new combination of targeted agents will be investigated. The combination is based on targeting angiogenesis, epithelial growth factor receptor (overexpressed in DIPG) and a downstream pathway; mammalian target of rapamycin (mTOR) concomitantly. This study consists of two phases. Depending on the maturation of the present study, and on preceeding therapy, an individual patient may enroll in phase a or phase a and b. Patients are separately asked informed consent for performing a biopsy: apart from histological confirmation, the tissue will also be used for retrospective correlation of DNA/RNA amplification or mutation and protein expression and clinical response. With regard to performing biopsies on DIPG-patients; the past five years biopsies have been taken regularly from DIPG-patients in France (Roujeau 2007) without mortality and 8% transient morbidity.

Study objective

Phase A:
Primary objective: Determining the feasibility of gemcitabine as a radiosensitizer in DIPG
Secondary objective: Evaluation of efficacy in terms of clinical and radiological response rate and progression free survival
Tertiary objectives: Evaluation of quality of life (QOL)

Phase B:
Primary objective: Determining the feasibility of adding erlotinib and everolimus to bevacizumab and irinotecan, based on two dose levels
Secondary objective: Evaluation of efficacy in terms of median duration of survival from time of progression
Tertiary objectives:
- Response on MRI
- Evaluation of quality of life (QOL)
- Pharmacokinetics of erlotinib and everolimus

General exploratory objectives:
- Evaluate the contribution of MRS to MRI
- Translational research on tumor tissue (if informed consent is given)
- Proteomics in blood (if informed consent is given)

Study design

Phase A: non-randomised open-label single-arm phase I-II trial. Cohorts of 3 patients will receive local radiotherapy (54Gy) with escalating dose levels of gemcitabine, or until an MTD has been established, according to the following dose escalation table. The starting dose is 80% of the MTD in adults with GBM.

Phase B: Non-randomised open-label single-arm phase I-II trial. Drugs are given in 2-week lasting courses. Backbone therapy consists of irinotecan 125mg/m2 IV 2-weekly and bevacizumab 10mg/kg IV 2-weekly. Cohorts of 3 patients will receive escalating dose levels of erlotinib, or until MTD has been established. The starting dose is 80% of the MTD established in children.
After the MTD of erlotinib is established (or erlotinib is safe at both doses) everolimus is added. Cohorts of 3 patients will receive escalating dose levels of everolimus, or until MTD has been established. The starting dose is 80% of the MTD in children. If no DLT occurs during the first two courses of both drugs, patients will be treated in an expanded cohort on the same dose level, until progressive disease or death occurs

Intervention

At diagnosis (MRI): patients with a focal pontine tumor (and DIPG if separate informed consent has been obtained) are biopsied before starting treatment.

Chemoradiotherapy: Radiotherapy starts within two weeks after diagnosis, five times a week with a total dose of 54 Gy. Gemcitabine (radiosensitizer), dosed 140-200mg/m2 IV, is given once a week, for 6 weeks in total. Each gift will be given 24 hours before radiotherapy.

Combination treatment: Irinotecan 125mg/m2 IV and bevacizumab 10mg/kg IV are given 2-weekly on the same day. Everolimus (2-3mg/m2 PO) and erlotinib (60-85mg/m2 PO) should be taken daily.

Study burden and risks

This study has treatment related risks as common in pediatric oncology, but in our opinion, with regard to the current infaust prognosis, the chance of prolongation of survival or even curation outweighs the risks. Of importance is that all agents have been used in children before, and are administered at tolerable dosages as reported in several phase I/II studies. If toxicities occur, dosages are modified or drugs are discontinued as described in the

protocol.

Burden: Standard treatment is six weeks of radiotherapy. In this study, patients need an extra day in the hospital during irradiation to receive therapy. During combination therapy, they visit the hospital 2-weekly for IV administration and blood collection. In addition, they have to take 2 drugs a a day orally. A medical history physical and neurological examination is performed weekly dring chemoradiotherapy and biweekly during combination therapy. Imaging is performed 3-monthly for response evaluation and and QOL assessments take place 4-monthly. Separate informed consent is asked for a biopsy (in case of DIPG) and for collecting an extra tube for proteomics during a venapuncture.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Patients with newly diagnosed, unresectable grade II-IV pontine glioma.
- Age between 3 and 18 years
- Willingness to perform a pregnancy test in females of child bearing age
- Written informed consent
- Platelet count * 100 x10 9/L (transfusion independent)
- Peripheral absolute neutrophil count (ANC) * 1.0 x10 9/L
- Direct bilirubin * 1.5 x upper limit of normal (ULN) for age
- SGPT (ALAT) < 5 x upper limit of normal (ULN) for age.
- Adequate Renal Function Defined As:
- Serum creatinine * 1.5 x upper limit of normal (ULN) for age;Phase B: patients with progressive disease after radiotherapy

Exclusion criteria

- Pilocytic (grade 1) astrocytomas
- Cervicomedullary junction tumors
- Presence of diffuse leptomeningeal disease.
- Performance status (Lansky or Karnofsky score) of 40% or less
- Life expectancy of less than six weeks without further therapy
- Pregnant or breastfeeding
- Other contra-indications for chemotherapy
- Neurofibromatosis type I

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	01-04-2011
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	avastin
Generic name:	bevacizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	campto
Generic name:	irinotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	gemzar
Generic name:	gemcitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	tarceva
Generic name:	erlotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-09-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2011

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2018
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	EUCTR2009-016080-11-NL
CCMO	NL29951.029.10

Study results

Date completed:	01-11-2019
Actual enrolment:	9

Summary results
Trial ended prematurely