Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.

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PRIMARY OBJECTIVESthe assessment if survival in grade III glioma without combined 1p/19q loss is improved by - daily temozolomide chemotherapy during radiotherapy - the administration of temozolomide after the end of radiotherapy SECONDARY...

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

Summary

ID

NL-OMON41635

Source
ToetsingOnline

Brief title
CATNON

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
anaplastic glioma without 1p/19q deletion, grade III non-1p/19q deleted glioma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)

Source(s) of monetary or material Support: EORTC/MSD,Merck Sharp & Dohme (MSD)

Intervention

Keyword: grade III glioma, non-1p/19q co-deleted, radiotherapy, temozolomide

Outcome measures

Primary outcome

overall survival as measured from the day of randomization (section 8.2.1.1,

page 38)

Secondary outcome

progression free survival, neurological progression free survival as determined

with the WHO Performance status, cognition as assessed with the Mini Mental

Status Examination (MMSE) and with the use of a short neuropsychological

testbattery, toxicity of temozolomide treatment (chapter 7) and quality of life

assessed with the EORTC QOL C30 questionnaire and the Brain Cancer Module

(chapter 10, chapter 8).

Study description

Background summary

Each year about 1000 new glioma are diagnosed in the Netherlands, in about 20% this concerns a grade III tumor. The median survival of these patients varies between the 2 and 6 year, depending on prognostic factors. The standard of care for these patients consists of radiotherapy to involved fields. However, concomitant and adjuvant chemotherapy with temozolomide plays an increasing role in the early management of these tumors. Ultimately, the outcome of patients with this disease is poor, with a fatal outcome being the rule.
Recent research has shown that adjuvant PCV chemotherapy does not improve the overall survival of newly diagnosed grade III glioma both with and without combined 1p/19q deletion, although it does improve progression free survival. These studies have also shown that the presence or absence of combined 1p/19q deletions is the most important prognostic for survival in thse tumors. The

median survival of patients without combined 1p/19q deletion was shown to be 2 to 3 year, in contrast to 6-7 years for patients with combined 1p/19q loss.

Inother clinical trials is was demonstrated that concurrent and adjuvante temozolomide chemotherapy improves survival and progression free survival in grade IV glioma or glioblastoma multiforme. This effect was predominantly observed in patients with tumors with methylation of the promoter of the MGMT gen, for which reason these tumors can no longer express alkyltransferase (a major resistance protein against alkylating andmethylating cytostatic agents like temozolomide). Because of the design it is not possible to asses which part of the treatment improves survival: the part with concurent radio-chemotherapy, the adjuvant part or both. The assessment of this is of high clinical relevance, as it may shorten treatment considerable.

In view of these studies the questions arises if concurrent and adjuvant temozolomide chemotherapy also improves survival in grade III glioma (anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic oligodendroglioma). Because of the large difference in outcome between patients with and without combined 1p/19q loss different studies will be developed for these patients. The present study will also assess if a prolongation of progression free survival has favourable effects onthe functioning of the patient.

It is expected that this study will determine if combined chemo-irradiation is also indicated in newly diagnosed grade III glioma without combined 1p/19q loss. At this moment different these tumors are treated differently in different institutions, either with or without temozolomide chemotherapy. Both approaches are currently viewed as the standard of care for these patients. It is therefore of high clinical interest to determine the impact of the addition of temozolomide to radiotherapy in this disease.

In this trial the duration of adjuvant treatment has been set on 12 months. This is clinical practice in many institutions, although others use 6 months. This duration has also been selected to allow a maximum beneficial impact on progression free survival.

Study objective

PRIMARY OBJECTIVES
the assessment if survival in grade III glioma without combined 1p/19q loss is improved by
- daily temozolomide chemotherapy during radiotherapy
- the administration of temozolomide after the end of radiotherapy

SECONDARY OBJECTIVES
in patients with grade III glioma without combined 1p/19q loss
- the determination of the administration of concurrent and adjuvant

temozolomide improves the progression free survival
- the assessment of the safety of concurrent and adjuvant temzolomide in patients with this tumor, including the assessment of the occurence of delayed neurotoxic effects
- the assessment of effects on the quality of life of concurrent and adjuvant temozolomide chemotherapy

(page 17)

Study design

Randomised phase III study with a 2 x2 design, with a randomization between
- radiotherapy with further treatment (which may include temozolomide) at progression
- radiotherapy with concurrent temozolomide chemotherapy
- radiotherapy with adjuvant temozolomide chemotherapy for 12 months
- radiotherapy with both concurrent and adjuvant temozolomide chemotherapy

(chapter 4, page 20)

Intervention

- All patients will receive radiotherapy on the tumor area to a dosage of 60 gy in 30 fracties

- For patients randomized to concurrent temozolomide chemotherapy: daily 75 mg/m2 during radiotherapy (including the weekends), with cotrimoxazol for PCP prophfylaxis

- For patients gerandomized to adjuvant temozolomide chemotherapy: 12 cycles with 150-200 mg/m2 temozolomide day 1-5 every four weeks.

(chapter 5)

Study burden and risks

The treatment that is investigated in this study is considered standard of care for patients with glioblastoma multiforme, the most frequent high-grade primary brain tunmor in adults. Combined chemo-irradation is also increasingly being used foir the patients with a tumor that is being investigated in the present study.
The most important side-effects of temozolomide chemotherapy are myelosuppression with thrombopenia and leukopenia. During concomittant chemo-radiotherapy with daily temozolomide pneumocystis carinii infections have been observed, for which reason prophylaxis with cotrimoxazol is indicated.
It is unknown if after prolonged follow-up combined radiotherapy and daily

temozolomide reulsts in anincrease of delayed leukoencephalopathy, with an increase of cognitive disturbances. This investigation of these disturbances is one of the objectives of this trial.
The follow-up schedule that is being used in this trial ican be considered as a standard follow-up schedule for patients with high grade glioma (chapter 6).

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

AT REGISTRATION:;- Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis;- Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review.;- WHO performance status 0-2;- Age >= 18 years;- All patients must use effective contraception if of reproductive potential. Females must not

be pregnant or breast feeding;- Absence of known HIV infection, chronic hepatitis B or hepatitis C infection;- Absence of any other serious medical condition that can interfere with follow-up;- Absence of any medical condition which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction);-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;RANDOMIZATION:;The combination of Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis AND Absence of combined 1p/19q loss both of which must have been determined by either local testing or central review;- Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review;- WHO performance status 0-2;- Age >= 18 years;- Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression;- Start of radiotherapy within 8 days from randomization;- Start of radiotherapy within 7 weeks (49 days) from surgery (extra 2 days could be allowed);- Patients must be on a stable or decreasing dose of steroids for at least two weeks;- Adequate hematological, renal and hepatic function;- All patients must use effective contraception if of reproductive potential. Females must not be pregnant or breast feeding;- Absence of known HIV infection, chronic hepatitis B or hepatitis C infection;- Absence of any other serious medical condition that could interfere with follow-up

Exclusion criteria

REGISTRATION:;- Previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to registration, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix.;- Prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®);- Prior radiotherapy to the brain;RANDOMIZATION:;- Prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®);- Prior radiotherapy to the brain

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-11-2007
Enrollment:	70
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	24-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-10-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2007
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	30-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2006-001533-17-NL
ClinicalTrials.gov	NCT00626990
CCMO	NL14970.078.07