Withdrawal of antiepileptic drugs in low grade and anaplastic glioma patients after long-term seizure freedom

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Primary Objectives: To identify the rate of successful AED withdrawal in LGG and anaplastic glioma patients with epilepsy and long-term seizure freedom after anti-tumour therapy.
Secondary Objectives: - Exploring the physician*s and patient*s...

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

Summary

ID

NL-OMON41523

Source
ToetsingOnline

Brief title
Withdrawal of AEDs in glioma patients

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Epilepsy in brain tumour patients

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Antiepileptic drugs, Glioma, Seizure

Outcome measures

Primary outcome

Study parameters include:

- physician*s decision and decision related arguments to continue AEDs despite fulfillment of all in- and exclusion criteria

- shared decision on AED continuation or withdrawal and decision related arguments

- start date of AED withdrawal, point of complete AED withdrawal, changes in AED type or dose (where applicable)

- seizure recurrence

- tumour symptoms, additional anti-tumour treatment and tumour recurrence

- treatment related adverse effects.

Secondary outcome

Not applicable

Study description

Background summary

Epilepsy is common in patients with brain tumours with incidence rates from 20-85%, depending on tumour type. Slowly growing tumours, mainly consisting of low grade gliomas (LGGs) and anaplastic gliomas, are most epileptogenic. A decrease in seizure frequency is known to contribute to less morbidity and improved quality of life. LGGs and anaplastic gliomas are associated with substantially longer survival compared to glioblastoma multiforme. Therefore, sustained seizure control in these patients is an important part of the brain tumour treatment.

Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment. Apart from the AEDs, the anti-tumour treatment which currently consists of surgery, radiotherapy and/or chemotherapy, largely contributes to a reduction in seizure frequency. In patients with seizure freedom after anti-tumour therapy the question raises whether AEDs should be continued endlessly, particularly because AEDs may cause side effects and negatively impact neurocognitive functioning and quality of life. Small observational studies on AED use in meningioma and LGG patients show ongoing seizure freedom after AED withdrawal in a majority of patients. However, knowledge about the feasibility of AED withdrawal after anti-tumour therapy and the effect on seizure frequency in glioma patients is currently lacking. In patients with non-tumour-related epilepsy AED use is generally discontinued after a prolonged period of seizure freedom. We think a similar decision is justified in glioma patients, particularly those with both long-term stable disease activity and prolonged seizure freedom.

We propose to explore the possibility of AED withdrawal in LGG and WHO grade III glioma patients with seizure freedom after anti-tumour therapy and without signs of tumour activity for at least one year. The decision to withdraw AEDs will be effectuated provided that the treating physician and the patient both agree on this decision. Otherwise, the existing AED regime will be continued. The decision to continue or withdraw AEDs and the subsequent effect on seizure frequency will be closely monitored in all patients. As the possibility of AED withdrawal is explored in a carefully selected group of glioma patients, this study may contribute to a more tailored AED treatment and prevent unnecessary and possibly harmful AED use in glioma patients.

Study objective

Primary Objectives: To identify the rate of successful AED withdrawal in LGG and anaplastic glioma patients with epilepsy and long-term seizure freedom after anti-tumour therapy.

Secondary Objectives:
- Exploring the physician*s and patient*s decision to either continue or withdraw AEDs after prolonged period of seizure freedom.
- Prospective monitoring of ongoing seizure freedom and AED treatment from the point of decision of AED withdrawal or continuation.
- Evaluating the association between seizure recurrence and tumour recurrence
- Evaluating treatment-related adverse events

Study design

Patients with a histologically confirmed LGG or anaplastic glioma treated in the VUmc, Medical Centre Haaglanden (MCH) or Erasmus MC will be included. Patients with epilepsy, stable disease and seizure freedom one year after

anti-tumour therapy will be included, as well as patients with non-acute symptomatic post-operative or post radiation seizures when seizure freedom exists for at least two years.

The investigator explores which patients experience seizure freedom as described above and are eligible for inclusion. Before the possibility of AED withdrawal will be discussed with the patient, the treating physician (mostly the neuro-oncologist) must consider the patient appropriate for withdrawal. AEDs will be continued when the physician finds any clinica disadvantages in AED withdrawal (e.g. due to status epilepticus in medical history, high morbidity risk with recurrent seizures). Physician*s objection*s against AED withdrawal will be recorded. When the patient fulfills all in- and exclusion criteria (see 4.2) and the physician has no objections to withdraw, the decision will be discussed at the next regular appointment at the out-patient clinic. The patient and the treating physician subsequently make a shared decision on the preferred AED treatment (continuation or withdrawal). In case of reluctance to discontinue AEDs, patient*s and/or physician*s arguments against withdrawal are explicitly recorded. AEDs are withdrawn according to a fixed schedule.

Patients will be divided in 2 groups: one in which AEDs are continued and the other in which AEDs are withdrawn. Follow-up in patients that withdraw AEDs takes place 6 weeks and 3 months after start of withdrawal. Patients that continu AEDs will have standard follow-up depending on tumour type and symptoms, usually every 6 months. During follow-up data about AED treatment, including start of AED withdrawal and completion of withdrawal where applicable, as well as data about seizure frequency and type, adverse effects and brain tumour symptoms and its treatment will be collected. The follow-up is part of the regular treatment of LGG and anaplastic glioma patients at the outpatient clinic. In case of seizure recurrence, AEDs will be adapted or restarted according to the expertise of the treating physician.

Study burden and risks

The proposed withdrawal of AEDs is a widely used practice in patients with seizures without a brain tumour. We think that the benefits of withdrawing AEDs in LGG patients may outweigh the disadvantages of endless AED continuation, particularly in patients that experience seizure freedom for a prolonged period of time. AED reduction may contribute to a decrease in adverse drug reactions and improve cognition and quality of life. Given the antiepileptic effect of the anti-tumour therapy and relatively good prognosis in these patients, we consider the risk of seizure recurrence acceptably low to withdraw AEDs. Seizure recurrence might result in a status epilepticus or cause additional traumatic injuries. However, similar risks are present in case of renewed tumour growth, when seizure recurrence appears to be inevitable in most patients despite their AED treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

(1) adults (>18 years)
(2) histologically confirmed LGG or anaplastic glioma (WHO grade I pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma, and subependymoma; WHO grade II astrocytoma , mixed oligo-astrocytoma, oligodendroglioma; ependymoma; WHO grade III brain tumours (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligo-astrocytoma or anaplastic ependymoma))
(3) presence of epilepsy and treatment with AEDs
(4) past anti-tumour treatment (surgical resection, brain irradiation or temozolomide chemotherapy)
(5) stable disease with absence of clinical or radiological signs of tumour recurrence during the past year
(6) seizure freedom for at least 1 year counted from the date of first surgery, last day of first

irradiation or last day of first temozolomide chemotherapy cycle; OR seizure freedom for at least 2 years from the last non-acute symptomatic post-therapy seizure.

Exclusion criteria

Patients who underwent biopsy only.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-01-2014
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	25-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	23-04-2015
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
CCMO	NL43575.029.13