Seizure Treatment IN Glioma (STING): comparing a treatment strategy with levetiracetam versus treatment with valproic acid in glioma patients with a first seizure

Published: 11-09-2017
Last updated: 15-05-2024

The overall aim of this strategy study is to directly compare the effectiveness of treatment with levetiracetam or valproic acid in glioma patients with de novo seizures. In addition, we aim to examine the level of toxicity, the impact of seizures...

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

Summary

ID

NL-OMON50617

Source
ToetsingOnline

Brief title
Seizure treatment in glioma

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
glioma, Primary brain tumor

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Crowdfunding

Intervention

Keyword: Glioma, Levetiracetam, Seizures, Valproic acid

Outcome measures

Primary outcome

The percentage of patients with ongoing seizure freedom at 6 months.

Secondary outcome

- Time to 6 month seizure freedom

- Seizure outcome at 12 months, according to the ILAE outcome classification

scale

- Level of toxicity and hospitalization rate due to treatment failure

- HRQoL, anxiety/depression, cognitive complaints, and performance status

- Burden of epilepsy

- Treatment response (e.g., maximum dosage of AED, use of add-on AED)

- Progression-free and overall survival

Study description

Background summary

Gliomas are the most common malignant primary brain tumors, with an annual incidence of 6 cases per 100.000 persons. Despite the fact that gliomas are a relatively rare malignancy, they result in a disproportionate share of cancer morbidity and mortality. To date, multimodal treatment with surgery, chemotherapy and radiotherapy does not result in cure, although prolongation of (progression-free) survival can be achieved. Median survival rates range from 15 months to more than 15 years, depending on tumor histology and molecular

parameters.

Epileptic seizures are a common symptom in patients with gliomas. The chance of developing a seizure depends on the tumor type, tumor location and its proximity to the cortical gray matter. In general, the epileptogenicity of the tumor is inversely related with its growth rate. In other words, low-grade gliomas (LGG) are more epileptogenic than faster growing tumors such as glioblastomas (GBM). Approximately 70-90% of all LGG patients present with epilepsy compared to 30-60% of high-grade glioma (HGG) patients.

Previous studies have shown that a reduction in seizure frequency is associated with less morbidity and improved health-related quality of life (HRQoL). Therefore, achieving sustained seizure control is one of the main goals of treatment in patients with brain tumor-related epilepsy. Both antiepileptic drugs (AEDs) and antitumor treatment may lead to seizure control. Nevertheless, treatment with AEDs may also cause side effects, which may have a negative impact on the patients* neurocognitive functioning and HRQoL. Moreover, enzyme-inducing AEDs may interfere with chemotherapeutic drugs and corticosteroids, leading to additional side effects. In due course, more than one third of patients will be refractory to AED treatment.

Guidelines recommend that patients with brain tumor-related epilepsy who experienced at least one seizure should receive anticonvulsant drug treatment until the tumor is controlled. If seizure freedom is achieved, tapering of AEDs could be attempted. In case of seizure recurrence, anticonvulsant treatment should be (restarted and) continued during the whole disease trajectory. The choice of drug is guided by various considerations, such as tolerability, adverse effects, and interactions with other agents, and no specific AED is recommended. Although there are no studies who support the use of a specific AED in brain tumor patients, the Dutch Society of Neurology recommends to use of non-enzyme inducing AEDs such as levetiracetam, valproic acid or lamotrigine. A second choice would be gabapentin or pregabalin. Due to their enzyme-inducing effect, interfering with chemotherapeutic drugs, treatment with carbamazepine, phenobarbital, phenytoine, oxcarbazepine and toparimate are not advised.

Currently, treatment of glioma patients with a specific AED mainly depends on the physicians* preference, as there is no robust evidence from randomized controlled trials supporting the use of one specific anticonvulsant above the other in glioma patients. The effect of the most commonly used AEDs, levetiracetam and valproic acid, on outcomes such as seizure freedom, toxicity, and HRQoL, and also on survival has been investigated, but results have been conflicting. This may be explained by small sample sizes and the retrospective study design of most studies. Nevertheless, better information is necessary for physicians to make evidence-based treatment decisions.

Study objective

The overall aim of this strategy study is to directly compare the effectiveness of treatment with levetiracetam or valproic acid in glioma patients with de novo seizures. In addition, we aim to examine the level of toxicity, the impact of seizures on HRQoL, performance status and survival.

Study design

In this strategy study, patients treated with levetiracetam or valproic acid will be compared. Glioma patients with a first seizure will be allocated by block randomization (stratified by follow-up frequency; 3-monthly follow-up or 6-monthly follow-up, as decided by the treating physician) to treatment with levetiracetam (arm A) or valproic acid (arm B).
In case of insufficient response on initial treatment, patients go the next treatment step as described in the protocol. In treatment step 2-4, drug dosage will be increased and in step 5 another anticonvulsant will be added. The choice of this add-on drug is based on the preference of the treating physician. In case of failure on step 5, further treatment will be initiated according to the physician*s preference. An insufficient response comprises toxicity or ineffectiveness. Toxicity is defined as grade 2 or higher according to the Common Toxicity Criteria for Adverse Events (CTCAE version 4.0) and ineffectiveness as having a seizure despite treatment with AEDs.

Intervention

Patients will receive either levetiracetam (brand name: *Keppra*) or valproic acid (brand name: *Depakine*) for treatment of epileptic seizures.

Study burden and risks

There are no direct benefits for the patients participating in this study. Nevertheless, their participation will contribute to a better understanding of the effectiveness of treatment with levetiracetam or valproic acid in glioma patients. Results of this study may provide the physician with better information, which may facilitate the choice of a specific AED and subsequently improve seizure treatment in this specific patient population.
In current daily clinical practice, patients receive either levetiracetam or valproic acid, suggesting that there will be no additional risk for patients (besides known adverse effects that are related to the drugs) participating in this study. However, it will cost the participants time to complete the questionnaires. Nevertheless, since follow-up is not that frequent and visits will be integrated with their regular visits to the neuro-oncology outpatient clinic, the participant burden is believed not to be substantial.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically proven or suspected diffuse astrocytoma (Isocytrate Dehydrogenase-1 (IDH-1) wildtype or IDH-1 mutated), diffuse oligodendroglioma (IDH-1 mutated and 1p/19q co-deleted), anaplastic astrocytoma (IDH-1 wildtype or IDH-1 mutated), anaplastic oligodendroglioma (IDH-1 mutated and 1p/19q co-deleted), glioblastoma (IDH-1 wild-type or IDH-1 mutated), or diffuse astrocytoma not otherwise specified (NOS), anaplastic astrocytoma NOS, oligodendroglioma NOS, oligoastrocytoma NOS, anaplastic oligoastrocytoma NOS, anaplastic oligodendroglioma NOS or glioblastoma NOS.
- Adult patients: >=18 years of age
- First epileptic seizure, no longer than 4 weeks ago. Also patients with a glioma, who have had tumor-related epilepsy in the past, can be included if they have been seizure-free for >=2 years without the use AEDs

- Monotherapy with antiepileptic drugs is considered most appropriate at the time of randomization
- Willing to provide written informed consent

Exclusion criteria

- Treated with antiepileptic drugs for the past 2 years, except emergency treatment in the past 4 weeks
- History of non-brain tumor related epilepsy
- Pregnancy
- Presence of contra-indications for use of levetiracetam or valproic acid

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2018
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO

Date:	11-09-2017

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22812
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL62477.058.17
OMON	NL-OMON22812