TKI concurrent with cerebral radiation therapy
Dutch: TKI tegelijkertijd met bestraling van de hersenen

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TKI concurrent with cranial radiotherapy (WBRT/SRT) does not increase acute and delayed neurotoxicity

Ethische beoordeling	Niet van toepassing
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON28884

Bron
NTR

Verkorte titel
SATIN

Aandoening

NSCLC; brain metastases; cranial radiotherapy; concurrent treatment; neurotoxicity

niet-kleincellig longkanker; hersenmetastasen; bestraling van de hersenen; gelijktijdige behandeling; neurotoxiciteit

Ondersteuning

Primaire sponsor: Maastricht UMC+
PO Box 5800 6202 AZ Maastricht
The Netherlands
Overige ondersteuning: Roche, Boehringer Ingelheim, AstraZeneca

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Increase in incidence of acute severe toxicity (per TKI) 2 weeks after completion of cranial radiotherapy, measured with CTCAE v 4.0, compared to baseline data

Increase in neurotoxicity 4 months after completion of cranial radiotherapy compared to baseline data

Toelichting onderzoek

Achtergrond van het onderzoek

SUMMARY

Rationale:

Non-small cell lung cancer (NSCLC) is one of the major causes of cancer related mortality worldwide.

Increasingly, new molecular features of NSCLC are being discovered, leading to an unprecedented growth of targeted agents, such as tyrosine kinase inhibitors (TKIs). Currently, TKIs are approved for metastasized NSCLC patients with a driver mutation (EGFR, ALK, ROS1). Approximately 20-35% of these patients are diagnosed with brain metastasis at initial diagnosis and are often amenable for initial treatment with a TKI. A relatively high percentage will also develop new brain metastases or progression of brain metastases during the course of their disease, often while on TKI treatment.

In patients with brain metastases both whole brain radiotherapy (WBRT) and stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT) can be considered as a local therapy. Neurotoxicity after brain radiotherapy is especially seen with WBRT, but also SRT. The radio-induced neurocognitive impairment evolves in a biphasic pattern: a subacute transient decline with a peak at four months, and a late delayed irreversible impairment several months or years after completion of WBRT. However, these results were obtained in unselected patients with often a poor overall prognosis, and it is not clear whether the deterioration resulted from radiotoxicity or intracranial progression. Moreover, the brain metastases itself can cause neurological complaints, also before initiation of radiotherapy. Patients with a driver mutation have a superior prognosis compared to those without, even in

the presence of brain metastases. It has also been suggested that EGFR-mutated and ALK-translocated NSCLC cells have a higher radiosensitivity than wildtype NSCLC but it is unclear what the impact is on neurotoxicity after cranial radiotherapy.

In current guidelines, no advice regarding TKI use during cranial radiotherapy is given. As the TKI may still be active on extra-cranial sites, clinicians are faced with the question whether to continue the TKI or not. Especially because rapid flare of the disease is a known phenomenon after interruption of a TKI. Preclinical studies suggest that TKIs enhance radiation effects but the effects on normal tissues are unclear.

In daily practice TKI's are given concurrent with cranial radiotherapy or they are discontinued during cranial radiotherapy because of (neuro)toxicity concerns, depending on the treating physician. When the TKI's are being discontinued, they are stopped for approximately one week before, during and one week after the radiotherapy (i.e. approximately 3 weeks) with the risk of a systemic disease flare-up.

Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up.

As cranial radiotherapy will be indicated for a significant number of these patients we want to extensively evaluate neurotoxicity in patients with a driver mutation, treated with concurrent brain radiotherapy and a TKI. Even though this concurrent treatment is rapidly becoming standard practice, detailed neurotoxicity data are not available for this patient group.

Objectives:

Primary Objectives:

- To assess whether there is acute severe toxicity (per TKI) 2 weeks after completion of cranial radiotherapy measured with CTCAE v 4.0.

- To assess whether there is an increase in neurotoxicity 4 months after completion cranial radiotherapy.

Secondary Objectives:

- To assess whether there is an increase in neurotoxicity 6 months after completion of cranial radiotherapy.

Exploratory:

- To assess what the brain penetration potential is, measured by the unbound brain-to-plasma ratio (Kp,uu), before and 2 weeks after cranial radiotherapy and to correlate these ratio with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy.

- To assess the plasma concentration of the TKI before and 2 weeks after cranial radiotherapy and to correlate this concentration with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy

- To assess what the intracranial PFS is at 4 and at 6 months after completion of cranial radiotherapy.

Study design:

Phase IV trial

- Duration: 2 year per TKI

There will be different cohorts, every TKI will be assessed separately. (erlotinib, gefitinib, afatinib, osimertinib, crizotinib, ceritinib, alectinib, crizotinib). For every TKI there is a WBRT (N=10) and a SRT (N=10) cohort. Patients are already treated with a TKI, the TKI is not part of the study. Patients are already scheduled for WBRT/SRT, this decision is not influenced by this trial. When a new TKI becomes available a new cohort will open and an amendment will be presented.

o Duration per patient will be approximately 6 months.

o Normally about 20 patients with a driver mutation are seen in 1 year at 1 centre. Of these patients about 5 will develop brain metastasis and are eligible for the study. There will be 5 centres that participate.

- Setting: the 5 centres (MUMC, VUmc, NKI/ AVL, UMCG, Erasmus MC) that are NVALT acknowledged as specialised driver mutation centers.

Study population:

NSCLC patients with driver mutation, treated with TKI, development of brain metastasis during TKI treatment, already scheduled for WBRT/SRT.

Intervention:

Standardized neurocognitive examination will be done before radiotherapy, after 4 months

and after 6 months. This will be measured by the following tests: neurological examination, HVLT-R, Trail making test part A and B, Controlled Oral Word Association, Digit symbol Subtest of the WAIS III and grooved Pegboard. A magnetic resonance imaging (MRI) of the brain will be performed at 4 and at 6 months (partly already usual care). Optionally cerebrospinal fluid (CSF) will be obtained by lumbar puncture before and two weeks after radiotherapy. Optionally blood will be obtained by venepuncture before and two weeks after radiotherapy.

Main study parameters/endpoints:

Primary endpoints:

Incidence of acute severe toxicity (per TKI) 2 weeks after completion of cranial radiotherapy, measured with CTCAE v 4.0

Neurotoxicity 4 months after completion of cranial radiotherapy

Secondary endpoints:

Neurotoxicity 6 months after completion of cranial radiotherapy

Exploratory:

Intracranial PFS 4 and 6 months after completion of cranial radiotherapy

CSF concentration of TKI before and 2 weeks after radiotherapy (optional for patients) in relation to acute toxicity (CTCAE v 4.0)

Plasma concentration of the TKI before and 2 weeks after cranial radiotherapy and to correlate this concentration with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The MRI and questionnaires that are used in this study are non-invasive except for a venapuncture to administer gadolinium-contrast for the MRI (and half of the MRIs are standard care for these patients). The risks of a MRI-scan are negligible because it is a magnetic field and does not involve ionizing. The venapuncture can cause a hematoma. The MRI will be performed twice (once already as standard care), preferably the same day as regular visits. Time per MRI is approximately 30 minutes. The neurocognitive testing will take about 60 minutes. This will also be done at the same day as regular visits.

Obtaining CSF by lumbar puncture is optional and is an invasive investigation. It will take

about 10 minutes and will be done by an experienced neurologist. As a possible complication of the puncture a temporary headache can occur.

Doel van het onderzoek

TKI concurrent with cranial radiotherapy (WBRT/SRT) does not increase acute and delayed neurotoxicity

Onderzoeksopzet

Intracranial PFS 4 and 6 months after completion of cranial radiotherapy

CSF concentration of TKI before and 2 weeks after radiotherapy (optional for patients) in relation to acute toxicity (CTCAE v 4.0)

Plasma concentration of the TKI before and 2 weeks after cranial radiotherapy and to correlate this concentration with toxicity (CTCAE v 4.0) 2 weeks after cranial radiotherapy

Onderzoeksproduct en/of interventie

baseline: physical examination, neurocognitive questionnaires, MRI (when not already performed as standard care), optional: blood/CSF

2 weeks after completion of cranial radiotherapy: physical examination, optional: blood/CSF

4 months after completion of cranial radiotherapy: physical examination, neurocognitive questionnaires, MRI (when not already performed as standard care)

6 months after completion of cranial radiotherapy: physical examination, neurocognitive questionnaires, MRI (when not already performed as standard care)

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

To be eligible to participate in this study, a patient must meet all of the following criteria:

- Stage IV NSCLC with driver mutation, treated with TKI, development of brain metastases during TKI treatment

- Indication for cranial radiotherapy determined by treating physician and radiation oncologist

- Age ¡Ý 18 years

- Ability to understand neurocognitive testing

- Written informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

A potential patient who meets any of the following criteria will be excluded from participation in this study:

- Prior radiotherapy to the brain when this precludes new radiotherapy.

- Neurologic/psychiatric illnesses (such as Alzheimer¡¯s disease)

- Claustrophobia

- Metal implants or other contra-indication for MRI

- Inability to lie supine for 30 minutes time (MRI)

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-07-2018
Aantal proefpersonen:	140
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 54721
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6518
NTR-old	NTR6707
CCMO	NL63377.068.17
OMON	NL-OMON54721

Resultaten