Effect of a reduced dose on cognitive side effects of enzalutamide in frail (m)CRPC patients

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Primary objectives- To determine the decrease in the CNS side effect fatigue* in frail (m)CRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after 6 weeks of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52805

Source
ToetsingOnline

Brief title
REDOSE

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
prostaatkanker

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: VGZ

Intervention

Keyword: Dose, Enzalutamide, mCRPC, Side effect

Outcome measures

Primary outcome

- The primary aim is to show that a reduced dose (120mg OD) results in less fatigue (measured by the change in FACIT-fatigue subscale score) after 6 weeks of therapy compared to the standard dose (160mg OD) for frail metastatic castration resistant prostate cancer patients.

Secondary outcome

- To explore if the change in FACIT-fatigue subscale score is different between the two arms of the study from start of therapy; an early measurement of fatigue is performed at 6 weeks, and to explore if there remains a difference between the two arms from baseline - up untill 6 months of therapy, the questionnaire is repeated after 6 months of therapy.
- To explore the change in FACIT-cognition subscale score over time: from baseline to 6 weeks, 12 weeks and 24 weeks after start of therapy between the two arms of the study (reduced dose vs standard dose)
- To explore the change in GDS-15 subscale score over time: from randomization to 6 weeks, 12 weeks and 24 weeks after start of therapy between the two arms of the study (reduced dose vs standard dose)
- To compare the percentage of patients that develop depression (score>5) on GDS-15 questionnaire between the two arms of the study (reduced dose vs standard dose) over time: after 6 weeks, 12 weeks and 24 weeks months after start if therapy

- To correlate the change in side effects with plasma concentrations (Ctrough)

of enzalutamide and N-desmethyl enzalutamide

- To evaluate the proportion (%) of patients in control arm (standard dose)

that remain on allocated dose level until the end of the study

- To evaluate treatment efficacy for both arms of the study according to PCWG3

Study description

Background summary

Prostate cancer is worldwide the second most commonly diagnosed cancer in men and also one of the most common causes of death related to cancer for men. Strategies to block androgen-receptor signaling have formed the backbone of prostate-cancer therapy since the first description of the hormonal dependence of this cancer in 1941. Androgen deprivation therapy results in tumor regression, relief of symptoms and a decrease in the concentration of prostate-specific antigen (PSA) in most patients. The understanding that castration resistant prostate cancer remains androgen driven changed the landscape of treatment for CRPC dramatically. Several hormonal therapy agents targeted to extragonadal androgen signaling pathways have been developed since 2010. Treatment efficacy was shown by abiraterone acetate and enzalutamide in patients with mCRPC.. This oral anti-androgen directed therapy allow patients unfit for chemotherapy to receive an effective though palliative therapy. Consequently the mCPRC patients treated today have more treatment options and are a generally older (median age 70) population with a vast amount of co-morbidities and co-medication. Side effects of these palliative therapies are important for quality of life of mCRPC patients. Fatigue/asthenia is one of the most frequently reported side effect of enzalutamide. The mechanism for these side effects is not yet fully understood but it was shown in rodent studies that enzalutamide and its active metabolite penetrate into the central nervous system (CNS). This might be related to the CNS side effects that were later seen in the phase 1 study where fatigue was found to be a dose-dependent adverse event. At dosages of 240mg and above an increasing proportion of patients required dose reductions due to side effects. After dose reductions the symptoms resolved. This was also found in a retrospective study of Japanese mCRPC patients (n=345) in which the side effects malaise and nausea decreased remarkably after dose reduction. Age>75 years was a predictor for side effects9. Furthermore in the post hoc analysis of the PREVAIL trial, a higher rate of falls (13.8% vs. 5.6%) was found for elderly patients (>75years) treated with enzalutamide compared to placebo (19.2% vs. 7.9%) indicating that

enzalutamide has a negative effect on the cognition in elderly. No exposure-response relation was observed in the study of Gibbons et al. Additionally, in a phase 1 trial of enzalutamide FDHT PET scans revealed that enzalutamide substantially displaced FDHT binding with a maximum effect seen at 150mg (corresponding with a Ctrough of 11,4 mg/L) was only minimally higher than seen at 60mg (corresponding with a Ctrough of 5mg/L)18. This suggests that androgen receptor binding may be saturated at serum levels of ~5-11,4 mg/L enzalutamide. Therefore, a minimum trough concentration of 5.0 mg/L could be considered as a target for exposure to enzalutamide.

Our hypothesis is that there is a relation between enzalutamide and or N-desmethylenzalutamide concentrations and CNS associated side effects such as fatigue. In particular, frail (m)CRPC patients are more prone for to develop CNS side effects on enzalutamide and that dose reduction to 75% (120mg) can be safely done to treat (m)CRPC in these patients with preserving optimal efficacy. No prospective trials on the effect of a priori dose reduction on CNS side effects has been published yet.

We aim to demonstrate that the patients treated at a reduced dose develop less side effects compared to the patients treated at the standard dose with maintenance of equivalent efficacy. Thereto, we designed an randomized controlled study in frail patients with (m)CRPC in whom we would like to explore if side effects such as fatigue, impaired cognition, worsened depression are affected by the enzalutamide dose (exposure).

Study objective

Primary objectives
- To determine the decrease in the CNS side effect fatigue* in frail (m)CRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after 6 weeks of treatment
Secondary objectives
- To determine the decrease in the CNS side effect fatigue* in frail (m)CRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after 12 weeks, and 24 weeks of treatment
- To determine cognition impairment** in frail (m)CRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after six weeks,12 weeks and 24 weeks of treatment
- To evaluate changes in depression score*** in frail (m)CRPC patients treated with a reduced dose of enzalutamide (120mg OD) compared to the standard dose of enzalutamide (160mg OD) after six weeks, 12 weeks and 24 weeks of treatment
- To correlate exposure (Ctrough) of enzalutamide and N-desmethylenzalutamide to the measured CNS side effects
- To determine the percentage (%) of subjects that remained on the allocated dose level until the end of the study
- To evaluate the effect of dose reduction on treatment efficacy according to

PCWG3
* facit-fatigue questionnaire
** facit-cognition questionnaire
*** geriatric depression scale 15 (GDS-15)

Study design

The study is a open label randomised (1:1) controlled phase IV study in 50 (25:25) frail (m)CRPC patients

Intervention

patients who are randomised to arm B of the study receive a reduced doser of enzalutamide (120mg) vs arm A (standard dose 160mg)

measurement of side effects: fatigue, cognition, depression

Study burden and risks

The risk-classification is assessed as negligible for the patients participating in this study. Enzalutamide is registered in the Netherlands for mCRPC patients. No exposure-response relation was observed in the study of Gibbons et al. Additionally, the phase I trial of enzalutamide showed that androgen receptor binding may be saturated at serum levels of ~5-11,4 mg/L enzalutamide, corresponding with 60mg to 150mg. Therefore, the reduced enzalutamide dose for the frail patients in this study will theoretically not result in underexposure and thereby suboptimal treatment outcomes, when plasma concentrations remain >= 5mg/L that was found in the phase I trial of enzalutamide. Thereto plasma concentrations of enzalutamide and N-desmethylenzalutamide are measured at 6 weeks, 12 weeks and 24 weeks. The dose will be adjusted instantly if the exposure is suboptimal (enzalumide concentration below 5 mg/L

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

- Frail* male patients with prostate cancer who will start treatment with enzalutamide
(* Frail is defined as a score on the comprehensive G8 assessment with cut-off <12 points
and score >grade 1 for Central Nervous Disorders according to the Common Toxicity Criteria Adverse Event (CTCAE) criteria, of one of the following:
Fatigue, Concentration impairment, cognitive disturbance, amnesia, depressed level of consciousness, memory impairment, hypersomnia.)
- Age at least 18 years
- Patient who are able and willing to give written informed consent prior to screening and enrolment
- Patients from whom it is possible to collect blood samples
- Patients who are willing to answer the questionnaires
- Life expectancy of > 6 months
- Capable of understanding and answering Dutch tests and questionnaires, as determined by the investigator

Exclusion criteria

- Other causes for cognition change (change in dose of opioids/sedatives/benzodiazepines) during last 2 weeks before study)
- Use of psychostimulantia such as methylphenidate within 1 week of start of study

- Diagnosed with medical conditions that affect cognition: Dementia, Alzheimer disease, Parkinson*s disease, psychiatric disorders that affect cognition other than depression or anxiety complaints related to the disease
- Active infection or other comorbidities that may contribute to fatigue or cognition change within 4 weeks of study entry
- Clinical relevant anaemia

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:	Recruitment stopped
Start date (anticipated):	18-06-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xtandi
Generic name:	Enzalutamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-11-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2019
Application type:	Amendment
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Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-01-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	23-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	Amendment
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2018-000779-33-NL
CCMO	NL65223.091.18