Repeated Rhenium-188-HEDP versus Radium-223-chloride in patients with metastatic castration-resistant prostate cancer: the RARE study.

Published: 22-02-2018
Last updated: 13-04-2024

The objective of this trial is to compare standard treatment with radium-223-chloride (proven surivval benefit) with treatment with rhenium-188-HEDP, which is nowadays only used for pain palliation. This trial includes patients with metastatic...

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

Summary

ID

NL-OMON48796

Source
ToetsingOnline

Brief title
RaRe

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
castration-resistant prostate carcinoma; prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: RaRe-studie: gefincancierd door zorgverzekeraars; Zilveren Kruis/Achmea;VGZ;CZ en Menzis. Side studie om extra bloedsamples te verzamelen: gefinancierd door het Liquid Biopsy Center(LBC) VUmc. RaRePET side studie: gefinancierd door een CCA grant (met toekenningsnummer CCA2018-5-45).,Zorgverzekeraar CZ,Zorgverzekeraar Menzis,Zorgverzekeraar VGZ,Zorgverzekeraar Zilveren Kruis/Achmea

Intervention

Keyword: bone metastases, castration-resistant prostate cancer, radium-223-chloride, rhenium-188-HEDP

Outcome measures

Primary outcome

The primary outcome of the study is the overall survival.

Secondary outcome

Secondary endpoints (main study)

- Time till PSA response

- Time till progression alkaline phosphatase

- Time till clinical progression

- Time till first skeletal related event

- Quality of life (comparison between both treatment arms)

- Pain response

- Incremental cost-effectiveness ratio (ICER); costs Quality Adjusted Life

Year (QALY)

Secondary endpoints (side studies)

- To collect blood samples (ctDNA, platelets and exosomes) for future research

- To determine the predictive value of 18F-DCFPyL PSMA uptake changes on PET/CT

for clinical response (e.g. progression vs. stable or partial metabolic

response) after the first radium-223-chloride or rhenium-188-HEDP therapy

(versus baseline), as defined in the PCWG2 criteria

- To correlate biochemical parameters changes (e.g. PSA, AF) with 18F-FCFPyL

PSMA uptake changes in metastatic lesions, during treatment.

(e.g. PSA, AF) with baseline 18F-DCFPyL PSMA uptake and changes in 18F-DCFPyL

PSMA uptake in tumor lesions during treatment

Study description

Background summary

Rhenium-188-HEDP is a bèta-emitting radiopharmacon connected to a bisphosphonate. This complex will accumulate in osteoblastic bone metastases after intravenous administration, and give local radiation to the metastases. Unlike external body radiotherapy, this treatment is also suitable for patients with multiple bone metastases. At this moment, the bèta-emitting radiopharmaceuticals are used for their pain palliative effect. The systematic review of Van Dodewaard et al. shows a relevant pain response in 60-80% of the patients treated with rhenium-188-HEDP.

Although the effect of rhenium-188-HEDP on survival has not been investigated yet, some studies suggest a survival benefit as well. Palmedo et al. randomized 58 patients between one or two injections of rhenium-188-HEDP. For both the progression free survival (7.0 months versus 2.3 months) as for the overall survival (12.7 versus 7.0 months), a significant benefit was seen for patients treated with two injections. These data are supported by some retrospective trials.

For the alfa-emitting radiopharmacon radium-223-chloride, a large phase III trial comparing radium-233-chloride with placebo has been performed. This trial showed a significant benefit in overall survival (median overall survival 14.9 months versus 11.3 months).Pain response was not an endpoint in this trial. The above mentioned review estimates the pain response for radium-223-chloride around 40-60% of the patients.

Rhenium-188-HEDP has some advantages compared to radium-223-chloride. Rhenium-188-HEDP can be produced in a generator on site (hospital), which ensures a fast availability. This 'own production' has a great impact on the cost; the estimated price for treatment of one patient with rhenium-188-HEDP is

around 5000 euro's, whereas the price for treatment with radium-223-chloride is around 30.000 euro's. In addition, the burden for patients is lower for rhenium-188-HEDP as this has to be administered three times with an 8-week interval (for radium-223-chloride this is six times with an interval of 4 weeks).Finally, the amount of patients with a pain response seems to be higher for rhenium-188-HEDP.

Study objective

The objective of this trial is to compare standard treatment with radium-223-chloride (proven surivval benefit) with treatment with rhenium-188-HEDP, which is nowadays only used for pain palliation. This trial includes patients with metastatic castration-resistant prostate cancer with progressive disease after two previous treatment (other than LHRH analogues) including docetaxel, or inability yo receive other treatments.

Both radiopharmaceuticals will be compared in terms of e.g. overall survival, pain palliation and quality of life and costs.

Study design

MAIN STUDY
This trial is randomized, open, multicenter phase III trial. Patients will be 1:1 randomized between
- 3 intravenous administrations of rhenium-188-HEDP 40 MBq/Kg (with a maximum of 3300 MBq) with an 8-weeks interval (experimental arm)
- 6 intravenous administrations of radium-223-chloride 55 kBq/kg, with an 4-week interval (standard treatment)

Prior to start of treatment, a bone scintigraphy and CT-thorax/abdomen will be performed.

Patients will be stratified according to; including hospital, bone-scan index, previous treatment with enzalutamide/abiraterone and previous treatment with docetaxel.

Patients in both study arms will be seen every 4 weeks by their treating physician, including laboratory tests and the request to fill in 3 questionnaires (VAS, EORTC QLQ 15 and EORTC QLQ BM22).

Treatment will be continued until progressive disease, completion of treatment, unacceptable toxicity or death, whichever comes first. Follow up will continue until death (during regular visits).

SIDE STUDIES (optional)
- Additional blood sampling: 3 bloodsamples each time, at 3 different

timepoints (baseline, cycle 3, before cycle 6) Blood collection will take place during existing blood collection moments.
- Additional scanning: two 18F-DCFPyL PSMA PET/CT scans , at 2 different timepoints (1 week before cycle 1, 1 week before cycle 2)

Intervention

Administration of 3 intravenous injections of rhenium-188-HEDP 40MBq/kg with an 8-week interval (experimental arm)

Administration of 6 intravenous injections of radium-223-chloride 55 kBq/kg with a 4-week interval (control arm, standard treatment)

Study burden and risks

MAIN STUDY

Rhenium-188-HEDP group;
- six control visits every 4 weeks (same as standard treatment)
- three administrations of rhenium-188-HEDP (possibly in the Meander Medical Center in Amersfoort if administration is impossible in the including hospital, travel expenses will be compensated); 3 times less than standard treatment
- 3 questionnaires every 4 weeks (this is the only additional burden compared to standard treatment)

Radium-223-chloride (standard treatment)
- six control visits every 4 weeks
- six administrations of radium-223-chloride
- 3 questionnaires every 4 weeks (this is the only additional burden compared to standard treatment)

The greatest risk of this trial is the possibility that, however unexpected, there might be no survival benefit of rhenium-188-HEDP.
The most relevant adverse events are of hematological origin. Based on the literature, we expect a comparable toxicity profile of both radiopharmaceuticals, so we do not expect any additional risks for the experimental treatment arm.

SIDE STUDIES (optional)
We don't expect extra burden and/or risk associated with participation to collect extra blood samples, since the blood sampling will take place during existing blood collection moments. The burden and risk for the additional scans are considered minimal. Patients will receive a venous cannula for tracer injection, which might cause transient intravenous site discomfort or local hematoma. The total additional radiation burden in this category of patients (limited life expectancy and already undergo frequent imaging) in this side

study account to 16 mSv, which is in our opinion justified by the future mertis from the scientic knowledge that can be obtained from this study. The scans will be performed in VUmc, for this patients will be compensated. Patients will have no direct benefits from participating in the sides studies. However, extra blood collection and additional imaging will add to our knowledge for future prostate cancer research

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- male, 18 years and older
- histologically confirmed prostate cancer
- bone metastases (*6 lesions) with pathological uptake at bone scintigraphy
- WHO performance status *2

- life expectancy at least 6 months
- castration resistant disease (testosterone level *1.7nmol/L)
- Progression on or after two previous treatments (other than LHRH analogues) including docetaxel), or inability to receive other treatments.
- baseline PSA * 5 ng/ml with evidence of progressively increasing PSA
- symptomatic disease with either regular use of analgesic medication or treatment with external beam radiotherapy within the previous 12 weeks
- adequate renal and hematologic function
- written informed consent

Exclusion criteria

- treatment with chemotherapy within the previous 4 weeks
- treatment with abiraterone and enzalutamide within the previous 5 days
- Previous hemibody external radiotherapy
- systemic radiotherapy with radioisotopes within the previous 24 weeks
- malignant lymhpadenopathy * 3cm in short axis diameter
- presence of visceral metastases
- imminent of established spinal cord compression
- active uncontrolled infections
- history of another malignancy within the last 5 years except adequatly treated basal cell carcinoma of the skin
- any serious uncontrolled concomitant disease

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: Recruitment stopped

Start date (anticipated):	25-05-2018
Enrollment:	402
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	rhenium-188-HEDP
Product type:	Medicine
Brand name:	PSMA
Generic name:	18F-DCFPyL
Product type:	Medicine
Brand name:	Xofigo
Generic name:	radium-223-chloride

Ethics review

Approved WMO Date:	22-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2019
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
EudraCT	EUCTR2017-000699-27-NL
ClinicalTrials.gov	NCT03458559
CCMO	NL61477.029.17