Phase 2 multicenter study determining the response to Cabazitaxel in metastatic prostate cancer (mCRPC) patients with AR-V7 positive or negative circulating tumor cells (CTCs): CARVE

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Ethical review	Not approved
Status	Will not start
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43532

Source
ToetsingOnline

Brief title
Cabazitaxel in mCRPC patients with AR-V7 positive or negative CTCs

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
metastatic castration-resistant prostate cancer; metastatic hormone-refractory prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: bedrijf,Sanofi-aventis

Intervention

Keyword: Androgen receptor splice variants, Cabazitaxel, Circulating tumor cells, Metastatic castration-resistant prostate cancer

Outcome measures

Primary outcome

PSA response defined as a reduction of at least 50% from baseline during

therapy, confirmed after *4 weeks by an additional PSA evaluation.

Secondary outcome

Secondary endpoints include CTC response rate, progression-free survival and

overall survival, as well as toxicity and cumulative administered dose of

cabazitaxel in second and third-line therapy. Furthermore, we want to explore

the AR-V7 mRNA expression as well as mRNA expression of other splice variants

in CTCs. We will also explore the relationship between systemic cabazitaxel

exposure and response. Lastly, we want to confirm the impact of the AR-V7

status in CTC on outcome to abiraterone or enzalutamide.

Study description

Background summary

After failure on Docetaxel, which has been the standard first line therapy for patients with metastatic castration-resistant prostate cancer (mCRPC), three treatment options are currently available. No head-to-head comparisons have been done for the three therapies in second-line mCRPC treatment and as of yet, the optimal choice is unknown. Two of treatment options are directed against the androgen receptor (AR), enzalutamide and abiraterone. The third option is

cabazitaxel, a taxoid. Resistance to the anti-AR therapies is at least in part a consequence of signaling through constitutively active AR splice variants (AR-Vs) (1-8).
Because AR splice variants only occur after conversion to a castration-resistant tumor, and can be acquired during systemic therapy for mCRPC, analysis of the castration-naïve primary tumor is not informative in the setting of second-line treatment of mCRPC. Circulating tumor cells (CTCs) can be analyzed repetitively and in real-time. Recently, AR-V7 mRNA expression in CTCs was shown to be associated with lack of response to anti-AR therapy (9). AR-V7 mRNA expression does not seem to hinder response to cabazitaxel in our retrospective pilot study (Onstenk et al., submitted for publication).
Therefore we hypothesize that the mRNA expression of AR-V7 in CTCs assessed before start of second-line treatment for mCRPC is associated with PSA response rate to cabazitaxel in patients who have progressed to docetaxel.

Study objective

The primary objective of this study is to explore the PSA response rate to cabazitaxel in mCRPC patients who have progressed to docetaxel and to correlate the PSA response to AR-V7 expression in CTCs. Exploratory objectives include documenting the PSA response to cabazitaxel after enzalutamide or abiraterone treatment in initially AR-V7 negative patients, describing the toxicity of cabazitaxel in second and third-line treatment,exploring if response measured by CTC counts and PSA is related to systemic cabazitaxel exposure, and to confirm the impact of AR-V7 status in CTC on outcome to enzalutamide or abiraterone.

Study design

This is a multicenter phase 2 study. All patients will receive physician's choice of treatment.
AR-V7 negative patients who are treated with enzalutamide or abiraterone and experience disease progression, can then again enter the screening phase and, after additional eligibility check, subsequently be treated with cabazitaxel if *3 CTCs are present and AR-V7 mRNA expression is now detected.

Intervention

In all patients, 2 x 10 mL blood will be drawn for enumeration and isolation of CTCs at baseline.

If physician's choice is cabazitaxel, cabazitaxel will be administrated intravenously at a dose of 25 mg/m², during a one-hour infusion every 3 weeks, as well as continuous treatment with prednisone 5 mg orally twice daily, or 10 mg once daily, according to standard care. In these patients, an additional 2 x 10 mL blood will be drawn at start of fourth cycle of treatment for CTC

enumeration and isolation. Also, an additional 10 mL blood will be drawn for storage of plasma at baseline and before every cycle (i.e., every 3 weeks) for analyses of cell-free DNA (cfDNA) as part of a side-study. In patients treated with cabazitaxel, 4 x 5 mL blood (baseline; end of infusion, 2 and 6 hours after end of infusion) will be drawn for a pharmacokinetic side-study, to explore a cabazitaxel exposure effect relation.

In patients treated with therapy other than cabazitaxel, an additional 10 mL blood will be drawn for storage of plasma at baseline and at 12 weeks after start of treatment for analyses of cell-free DNA (cfDNA) as part of a side-study.

AR-V7 negative patients treated with abiraterone or enzalutamide that subsequently experience disease progression can again enter the screening phase of the study. An additional 2x 10 mL blood will be drawn for enumeration and isolation of CTCs, as well as 1x 10 mL for analysis of cell-free DNA (cfDNA).

Study burden and risks

For the CTC enumeration and isolation, a total of 20 mL additional blood will be drawn at baseline.. An additional 20 ml will be drawn 9 weeks after start of treatment. Furthermore, in AR-V7 negative patients an additional 20 ml will be drawn upon progression to abiraterone or enzalutamide.
For storage of plasma for cfDNA analysis, a total of 100 mL additional blood will be drawn at the time of regular blood draws (at baseline and before each treatment cycle) from patients treated with cabazitaxel. . Patients not treated with cabazitaxel will have a total of 30 mL additional blood drawn for storage of plasma for cfDNA analysis (at baseline, at 12 weeks after start of treatment, and upon disease progression).
For pharmacokinetic analysis, in patients treated with cabazitaxel, a total of 20 mL (4 x 5 mL) additional blood will be drawn at baseline, end of infusion, 2 and 6 hours after the first cabazitaxel infusion.
Cabazitaxel is standard second-line chemotherapy for mCRPC patients. In the TROPIC trial, the most common observed grade 3-4 toxicity was neutropenia (82%) (12). Despite the high incidence of neutropenia, febrile neutropenia was rare (8%). The most frequent non-hematologic adverse event (AE) was diarrhea, occurring in 47% (grade *3 6%) of patients treated with cabazitaxel, compared to 11% (grade *3 <1%) of patients treated with mitoxantrone. In the TROPIC trial, a total of 18 (5%) patients treated with cabazitaxel died within 1 month of the last drug infusion due to adverse effects. This compares to 3 drug-related deaths (2%) in the mitoxantrone group. The most common cause of death in patients treated with cabazitaxel was neutropenia and its clinical consequences. The frequency of hematological adverse events and related deaths demonstrates that cabazitaxel treatment requires careful monitoring and management of emerging symptoms. Dose reductions as well as supportive treatment (i.e. the administration of granulocyte colony-stimulating factor [G-CSF]) will be considered to manage the toxic effects of treatment.

Cabazitaxel treated patients will have scheduled study visits frequently, in accordance with standard-of-care cabazitaxel treatment. Patients will return for regularly scheduled study visits for as long as they continue study treatment, or discontinued study treatment but have not yet experienced disease progression. All patients will be followed for survival after discontinuing treatment. For the primary endpoint, serial blood samples will be collected every three weeks to quantify PSA. Radiographic evaluations (bone scans and CT/MRI-scans of the abdomen and pelvis) will be employed after four and eight cycles of cabazitaxel to assess the status of the disease according to modified RECIST 1.1 criteria.
The safety of cabazitaxel in second and third-line treatment will be assessed by monitoring the frequency of treatment related (serious) adverse events, which will be recorded according to the Common Terminology Criteria (CTCAE) scale version 4.03.

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

Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
- Continued androgen deprivation therapy either by LHRH agonists/antagonists or orchiectomy.
- Serum testosterone <50 ng/ml (1.7 nmol/L) within 21 days of treatment arm allocation.
- Age *18 years
- Disease progression during or after treatment with docetaxel. Disease progression for study entry is defined as one or more of the following criteria:
* At least 3 consecutive PSA rises over a reference value, with an interval of * 1 week between each determination. PSA at screening visit should be * 2.0 *g/l.
* Bone disease progression defined by the appearance of *2 new lesions on a bone scan (confirmed by a second bone scan 6 weeks later).
* Soft tissue disease progression defined by modified RECIST 1.1.
- ECOG performance status 0-2
- Written informed consent according to ICH-GCP

Exclusion criteria

- Impossibility or unwillingness to take oral drugs
* Geographical, psychological or other non-medical conditions interfering with follow-up
* Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus or active systemic or local bacterial, viral, fungal - or yeast infection)
* Symptomatic CNS metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent.
* Chemotherapy or immunotherapy (other than LHRH analogues) within the last 4 weeks before study inclusion.
* Prior treatment with cabazitaxel
* Successive treatment with both abiraterone and enzalutamide in the post-docetaxel setting
* Radiotherapy to 40% or more of the bone marrow
* Known hypersensitivity to corticosteroids
* History of severe hypersensitivity reaction (*grade 3) to docetaxel
* History of severe hypersensitivity reaction (*grade 3) to polysorbate 80 containing drugs
* Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 3A4/5 (a one week wash-out period is necessary for patients who are already on these treatments) (see Appendix C)
* Concomitant vaccination with yellow fever vaccine
* Abnormal liver functions consisting of any of the following (within 21 days before treatment group allocation):
* Total bilirubin > 1.5 x ULN (except for patients with documented Gilbert*s disease)
* If total bilirubin > 1 x ULN or AST > 1.5 x ULN inclusion is permitted but cabazitaxel dose should be reduced 20mg/m2

* Abnormal hematological blood counts consisting of any of the following (within 21 days before treatment group allocation):
* Absolute neutrophil count < 1.5 x 109/L
* Platelets < 100 x 109/L
* Hemoglobin < 6.2 mmol/L

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	100
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Jevtana
Generic name:	Cabazitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	07-01-2016
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	03-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-003629-33-NL
CCMO	NL55865.078.15