A single arm phase 2 multicenter study determining the response to Cabazitaxel in metastatic prostate cancer (mCRPC) patients with AR-V7 positive circulating tumor cells (CTCs)

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

Summary

ID

NL-OMON47078

Source
ToetsingOnline

Brief title
Cabazitaxel in mCRPC patients with AR-V7 positive CTCs (CABA-V7)

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

The primary endpoint is PSA response, defined as a *50% PSA decline from

baseline during therapy.

Secondary outcome

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

survival to cabazitaxel in AR-V7 positive patients, as well as toxicity and

cumulative administered dose of cabazitaxel in second and third-line therapy.

Furthermore, we want to explore the relationship between systemic cabazitaxel

exposure and response.

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), several treatment options are currently available. Two of the treatment options are directed against the androgen receptor (AR), enzalutamide and abiraterone. A third option is cabazitaxel, a next generation taxane. No head-to-head comparisons have been done for these three therapies in second-line mCRPC and as of yet, the optimal choice is unknown. Resistance to the AR-targeted therapies is at least in part a consequence of signaling through constitutively active AR splice variants (AR-Vs).

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 AR-targeted therapy (Antonarakis et al. N Engl J Med. 2014 Sep 11;371(11):1028-38). AR-V7 mRNA expression does not seem to hinder response to cabazitaxel in our retrospective pilot study (Onstenk et al. Eur Urol. 2015 Dec;68(6):939-45) nor in two recently published retrospective studies (Antonarakis et al. JAMA Oncol. 2015 Aug;1(5):582-9; Scher at al. JAMA Oncol. 2016 Jun 4).

Therefore we hypothesize that the mRNA expression of AR-V7 in CTCs assessed before start of second-line treatment for mCRPC does not affect PSA response to cabazitaxel in patients who have progressed to docetaxel.

Study objective

The primary objective of this study is to explore the PSA response to cabazitaxel in mCRPC patients who have progressed to docetaxel and have detectable AR-V7 expression in CTCs. Exploratory objectives include describing the toxicity of cabazitaxel in second and third-line treatment as well as exploring if response measured by CTC counts and PSA is related to systemic cabazitaxel exposure.

Study design

This is a multicenter, single arm phase 2 study.

Patients who are eligible to undergo second or third line treatment will be asked to undergo prescreening consisting of a CTC count and, in case *3 CTCs are detected, AR-V7 determination. Patients with *3 CTCs with AR-V7 expression will be asked to sign a second informed consent to enter the treatment study. In this study they will receive Cabazitaxel 25 mg/m² every 3 weeks plus prednisone 10 mg daily, and undergo repeated blood sampling for biomarker sample collection.

Intervention

During the prescreening in all patients, 2 x 10 mL blood will be drawn for enumeration and isolation of CTCs.

All patients with *3 CTCs with AR-V7 expression will be asked to sign consent for the treatment study.

All patients included in the treatment study will be administrated cabazitaxel

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. In the treatment study patients, an additional 2 x 10 mL blood will be drawn after the third cycle of treatment for CTC enumeration and isolation. An additional 10 mL blood will be drawn for storage of plasma at baseline and before start of every cycle (i.e., every 3 weeks) for analysis of cell-free DNA (cfDNA). Moreover, 4 x 5 mL blood (baseline; end of infusion, 2 and 6 hours after end of the first cabazitaxel infusion) will be drawn for pharmacokinetic studies, in order to explore a cabazitaxel exposure effect relation.

Study burden and risks

In patients who are in prescreening only and do not proceed to the treatment study, 20 mL additional blood will be drawn at the time of regular blood draws. In patients included in the treatment study a total of 40 mL additional blood will be drawn at the time of regular blood draws for CTC enumeration and isolation,. 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). In case of study treatment discontinuation without progression 10 mL additional blood will be drawn every 3 months until progression, death, or study cut off, whichever comes first.
For pharmacokinetic analysis 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. All other evaluations are part of the standard of care treatment.

Cabazitaxel is standard second-line chemotherapy for mCRPC patients. In the TROPIC trial, the most common observed grade 3-4 toxicity was neutropenia (82%). 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. The toxicity profile of cabazitaxel is well known and manageable in daily practice. In this study the treatment will not divert from the standard of care.

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.

The recent PROSELICA study, randomizing patients between a cabazitaxel dose of 20mg/m2 and 25mg/m2 in the second line treatment setting, presented at the 2016 ASCO Annual meeting, suggests that a dose reduction to 20mg/m2 might improve the toxicity profile and is results in equivalent progression free survival.
However, the data regarding the endpoint we chose (PSA response) showed a clear difference in favor of the 25mg/m2 group. Therefore, awaiting the full publication we choose to mandate a 25mg/m2 cabazitaxel dose for this study.

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 start (if patient enters treatment phase of the study)
- Age *18 years
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

* 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 of protocol)
* 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
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-02-2017
Enrollment:	125
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	07-09-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	26-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-002993-11-NL
CCMO	NL58639.056.16