A Phase I-IIa, Open label, Single Center, Dose Escalating Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of Intravenous Pegylated Liposomal Dexamethasone Sodium Phosphate as Monotherapy in Patients with Castration Resistant Metastatic Prostate Cancer

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To determine the tolerability, pharmacokinetics and pharmacodynamics of liposomal dexamethasone (Oncocort*) in patients with metastatic prostate cancer.

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

Summary

ID

NL-OMON45330

Source
ToetsingOnline

Brief title
Liposomal Dexamethasone in metastatic prostate cancer

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym

Metastatic Prostate Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Enceladus Pharmaceuticals B.V.
Source(s) of monetary or material Support: Enceladus Pharmaceuticals BV

Intervention

Keyword: Liposomal dexamethasone, Prostate cancer

Outcome measures

Primary outcome

Safety and tolerability

Assessed using adverse event reporting, standard clinical measures (vital signs, ECG), routine laboratory assessments and activation of complement during infusion.

Pharmacokinetic endpoints

Extensive PK sampling will be performed in each of the 10 patients after the first dose of 10 mg and after the first dose of 20 mg. Optionally, additional PK sampling will be performed, guided by PK data obtained in part I.

A validated bioanalytical assay will be used to determine the concentrations of liposomal and free dexamethasone in plasma after Oncocort administration. The following pharmacokinetic variables will be calculated, if possible:

- Area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC0-t) and from time 0 extrapolated to infinity (AUC0-inf);

- Maximal observed plasma drug concentration (Cmax);

- Time to maximum observed plasma drug concentration (tmax);

- Half-life (t *);

- Volume of distribution (Vd);

- Clearance.

Pharmacodynamic effect endpoints

- PSA;

- Bone marker: alkaline phosphatase;

- Cortisole;

- Sex steroids (testosterone, estradiol, FSH, LH and SHBG);

- Fasting blood glucose;

- Lymphocyte count;

- Activation of complement; AP and CP

- Comprehensiveness of bone metastases, as assessed in Scintigraphy/CT/MRI;

Secondary outcome

N/A

Study description

Background summary

Glucocorticoids are steroid hormones with anti-inflammatory and immunosuppressive activities. For over 30 years corticosteroids have been used in the management of castration resistant prostate cancer (CRPC). Initially, single agent prednisone 7.5*10 mg daily was used in the management of metastatic CRPC patients (mCRPC) and subsequent studies showed clinical benefit in these patients. In phase 3 trials the response rate of prostate-specific antigen (PSA) to prednisolone ranged from 9% to 33%, and the median time to PSA progression has ranged from 2 to 6.6 months.

Until recently, dexamethasone has been less well studied in the treatment of CRPC. Phase 2 studies of low-dose, daily dexamethasone have reported somewhat higher PSA response rates (50*60%), with median time to PSA progression of 7-8 months. The two largest studies, including a combined total of 237 patients treated with dexamethasone as a single agent, reported PSA response rates around 50%. In a recently reported trial, the group of Parker and De Bono reported a single-center randomised phase 2 trial comparing dexamethasone and prednisolone to explore the hypothesis that dexamethasone may be more active than prednisolone in the treatment of CRPC. Intention to treat analysis showed a confirmed PSA response in 41% of the patients for daily dexamethasone treatment versus 22% for daily prednisolone (p=0.08). In evaluable patients, the PSA response rates were 47% versus 24% for dexamethasone and prednisolone, respectively (p=0.05). Median time to PSA progression was 9.7 months on dexamethasone versus 5.1 months on prednisolone (hazard ratio: 1.6; 95% confidence interval, 0.9-2.8). In 43 patients with measurable disease, the response rate by RECIST was 15% and 6% for dexamethasone and prednisolone, respectively (p=0.6). Of 23 patients who crossed over at PSA progression on prednisolone, 7 of the 19 evaluable (37%) had a confirmed PSA response to dexamethasone. Clinically significant toxicities were rare. These data suggest that dexamethasone is more effective with a similar side-effect profile and may be the most efficacious corticosteroid monotherapy in CRPC patients. The higher antitumor activity for dexamethasone supports its use in the clinic in mCRPC patients and daily doses of 0.5 mg dexamethasone are regarded as standard for CRPC patients who require corticosteroid monotherapy.
The explanation for the superior activity of dexamethasone remains uncertain. However, it is plausible that differential anti-inflammatory activity and/or superior suppression of tumour-associated macrophages play a role. The inflammatory tumour microenvironment, and more specifically the tumour-associated macrophages, plays an essential role in the development and progression of prostate cancer towards metastatic bone disease. This may be further exploited by using liposomal formulations that utilize the so-called enhanced permeability and retention (EPR)-effect. Tumours are often characterized by a leaky vasculature, which - combined with the prolonged circulation time of liposomes - leads to efficient tumour localization of these drug carriers, via the so-called enhanced permeability and retention (EPR)-effect. Over the last few decades, tumour-targeted liposomal drug delivery has become an emerging therapeutic strategy. For specifically designed long-circulating liposomes it has been shown that intravenous administration results in accumulation in tumour tissue due to the EPR-effect.
The anti-cancer activity and utility of liposomal encapsulated dexamethasone versus free dexamethasone was studied in a preclinical model of human prostate cancer metastatic to the bone. Intravenously administered liposomes were shown to localize efficiently to bone metastases in vivo and treatment of established bone metastases with (liposomal) dexamethasone resulted in a significant inhibition of tumour growth up to 26 days after initiation of treatment. Furthermore, 1.0*mg/kg liposomal dexamethasone significantly outperformed 1.0* mg/kg free dexamethasone, and was found to be well-tolerated at

clinically-relevant dosages that display potent anti-tumour efficacy. Liposomal delivery of the dexamethasone inhibits the growth of malignant bone lesions and offers a promising new treatment option for advanced, metastatic prostate cancer which supports further clinical evaluation.

Study objective

To determine the tolerability, pharmacokinetics and pharmacodynamics of liposomal dexamethasone (Oncocort*) in patients with metastatic prostate cancer.

Study design

This exploratory, non-comperative, monocentre, open label, prospective stage I-IIa, dose escalating study of intravenous pegylated liposomal dexamethasone sodium phosphate (Oncocort*) monotherapy in patients with metastatic prostate cancer with the objective to assess safety, tolerability, pharmacokinetics, and pharmacodynamics after short-term treatment with repeated infusions.
We aim to treat ten mCRPC patients with bone metastases with a single dose of 10mg and 5 doses of liposomal Dexamethasone 20 mg (approximately equivalent to therapeutic dose of 0.5 mg oral dexamethasone daily), administered in two-weekly invervals.

Intervention

Oncocort*

Study burden and risks

The risks associated with the administration of Oncocort to humans have not yet been identified, because this compound has not yet been studied in humans. On the basis of data collected from preclinical investigations, the main target organ toxicity of Oncocort is considered to be related to the thyroid. Humans are much less sensitive to changes in thyroid hormones because their higher levels of thyroxine-binding proteins lead to slower hormone metabolism. As a safety measure thyroid hormones will be monitored in 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

1. Adult patients with mCRPC and one or more metastases in the bone, confirmed by bone scintigraphy, MRI or CT-scan within 6 weeks before first dosage;
2. Able to participate, and willing to give written informed consent and to comply with the study restrictions;
3. Body mass index (BMI) of 18 kg/m2 or higher (inclusive) and a minimum weight of 50 kg;
4. Not yet, or no longer being eligable for other, registered therapy other than corticosteroids.
5. Live expectancy in good clinical condition (WHO 0-1) and live expectancy of more than 3 months.

Exclusion criteria

1. Concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
2. Contraindication for glucocorticoids as judged by investigator
3. Use of systemic glucocorticosteroids within 4 weeks before first dosage, with exception of topical and inhalation steroids.
4. Any confirmed and clinically significant allergic reactions (urticaria or anaphylaxis; non-

active hay fever is acceptable). Allergy or hypersensitivity against any drug, including any component of the study drug, biologic therapy or IV radiocontrast agent.
5. Clinically significant abnormalities, as judged by the investigator, following a detailed medical history, a physical examination including vital signs, 12-lead ECG and laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant.
6. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder that may aggravate due to study participation and jeopardize the health status of the patient.
7. Any infection within 1 month prior to the anticipated dosing day.
8. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
9. History of alcohol or substance abuse
10. Use of CYP3A4-inhibiting drugs or food (grapefruit, grapefruit juice, grapefruit-containing products, Seville oranges, or pomelo-containing products, and quinine containing drinks within 11 days prior to day of dosing.
11. Participation in an investigational drug or device study within 3 months prior to screening.
12. Donation of blood over 500 mL within three months prior to screening.
13. Vaccination within 6 weeks prior to start of treatment or planned vaccination up to 90 days after the final dose.
14. Unwillingness or inability to comply with the study protocol for any other reason.
15. Expected fulminant progression of disease

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Oncocort
Generic name:	PEG-liposomal dexamethasone sodium phosphate

Ethics review

Approved WMO Date:	08-11-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	15-02-2018
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	EUCTR2016-003121-42-NL
CCMO	NL58731.056.16