Pilot study: Toxicity of oestradiol for adjuvant endocrine therapy in locally confined prostate cancer

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To analyse the safety of oestradiol in the setting of endocrine treatment for locally extended prostate cancer adjuvant to radiotherapy.

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

Summary

ID

NL-OMON50312

Source
ToetsingOnline

Brief title
OAT - Oestradiol adjuvant trial

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
Prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Achmea Gezondheidszorg

Intervention

Keyword: Adjuvant endocrine therapy, Locally confined prostate cancer, Oestradiol, Toxicity

Outcome measures

Primary outcome

Incidence of cardiovascular events (number of cardiovascular events per 100 patient years).

Secondary outcome

- Compliance to the study intervention (measured by oestradiol serum levels at every visit).

- Incidence of endocrine related side effects.

- Changes of metabolic serum parameters (liver function (SGOT, SGPT, bilirubin), endocrine (oestradiol, testosterone, PSA), lipid profile (HbA1c, cholesterol, HDL).

- Time to reach testosterone castration levels (during run-in period, T * 1.7 nmol/L).

- Quality of Life (EORTC QC 30, PR25 potency, overall).

Study description

Background summary

Endocrine treatment is the mainstay for metastatic prostate cancer. During the last three decades, medical castration has been chosen above surgical castration by orchidectomy. Current options involve predominantly the use of relatively expensive Luteinizing-hormone-releasing hormone (LHRH) agonists because of their reported preference with regard to the incidence of thromboembolic events when compared to oestrogens. [1] However, LHRH agonists (LHRHa) are associated with long-term toxic effects, including osteoporosis, and adverse metabolic changes. The use of parenteral oestrogen is under trial

in the PATCH-trial that reported recently on the intermediate long term effects of transdermal oestradiol application in men who require permanent androgen deprivation. The thromboembolic complications associated with transdermal oestrogen appear similar to that of LHRH agonists in this randomised study. [1] As parenteral oestrogen administration avoids the entero-hepatic circulation (first pass hepatic metabolism) it is associated with a reduced incidence of cardiovascular toxicity compared with oral oestrogen. [2] The recently updated prostate cancer guideline of the Dutch Urological Society, stated that though parenteral oestrogen treatment could be safe in patients without cardiovascular risk factors, further study is needed before this therapy might become standard care. [3] However, oestrogen treatment is already regularly prescribed by a lot of Dutch urologists (amongst which the urologists participating in the current trial) for androgen deprivation in patients with prostate cancer, also in the earlier phase of the disease. Treatment with oestrogens is reimbursed by the health care insurances.
During this study it will be analysed whether transdermal applied oestrogens in the earlier phase of the disease, that is during the adjuvant endocrine setting during curative treatment for locally extended prostate cancer, might even be less toxic compared to the standard medical castration therapy.

1. Langley, R.E., et al., Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). Lancet Oncol, 2013. 14(4): p. 306-16.
2. Turgeon, J.L., et al., Hormone therapy: physiological complexity belies therapeutic simplicity. Science, 2004. 304(5675): p. 1269-73.
3. Reijke, T.M.d., Richtlijn Prostaatcarcinoom, 2013: Oncoline.

Study objective

To analyse the safety of oestradiol in the setting of endocrine treatment for locally extended prostate cancer adjuvant to radiotherapy.

Study design

This pilot study is a multicentre, open label, non-randomized, intervention study.

Intervention

During a run*in period of approximately 3 months subjects will self-administer four skin patches for transdermal application of oestradiol (100 *g per 24 h) per time, which will be changed twice weekly. After the run-in period, a regimen of three oestrogen patches changed twice weekly will be given as soon as castrate testosterone concentrations (1.7 nmol/L or lower) have been

reached. Subjects will be treated with oestradiol patches for a period of two years.

Study burden and risks

The burden related to participation in this study are the two extra visits at week 0 and 4 (run in period), filling in questionnaires at 7 visits, and the extra blood/serum withdrawal for analysis of hormones and related metabolites and/or safety measurements (8.5 * 25 ml per withdrawal, 8 times). Weight and blood pressure (BP) are measured 7 times, otherwise no physical exams or tests will be done. Therefore the risks for this study with regard to extra tests are negligible.

Side effects expected based on information of the PATCH trial are:
- Cardiovascular (thromboembolism): 5%
- Gynaecomastia: 75% (several grades of severity)
- Hot flushes: 25%
- Dermatological problems: 42%

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) Men * 18 years.
2) Locally advanced prostate cancer.
3) Selected for at least two years of adjuvant endocrine therapy and EBRT.
4) Signed informed consent.
5) Testosterone serum level > 6 nmol/l.

Exclusion criteria

1) Current endocrine treatment or previous therapy within 6 months (5-alpha reductase inhibitors are permitted).
2) Previous radiological confirmed deep venous thrombosis or pulmonary embolus.
3) Cerebrovascular event (TIA or CVA) within 6 months.
4) Coronary heart disease within 6 months.
5) Instable angina pectoris within 6 months.
6) Congenital thrombofilic diseases.
7) Thrombolic disease within 6 months.
8) Heart failure as defined by NYHA class >2.
9) Hypertension (not corrected by medication) >160/100 mmHg. If either systolic or diastolic value is higher than these values the patient is not eligible.
10) Suboptimal regulated diabetes mellitus or de novo diabetes mellitus as defined by HbA1c of over 6,5% (48 mmol/mol).
11) Rheumatoid arthritis.
12) Impaired renal function as defined by a GFR < 30 ml/ min/1,73 m2
13) Acute liver failure or reduced liver function showing as increased serum parameters (SGOT, SGPT, bilirubine > 2.5 times normal).
14) Porfyria.

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):	08-09-2014
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Estradiol Sandoz patch
Generic name:	Oestradiol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-02-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	04-06-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-02-2015
Application type:	Amendment
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

ID: 20250
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2013-005479-42-NL
CCMO	NL47698.078.14
OMON	NL-OMON20250