153Sm-EDTMP versus docetaxel for multiple painful osseous metastases in prostate cancer

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The sequential application of chemotherapy and radionuclide treatment in patients with symptomatic osseous metastasized prostate cancer. Patients with more than one painful osseous metastasis will be randomized between 153Sm-EDTMP or docetaxel 3...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON30762

Source
ToetsingOnline

Brief title
153Sm-EDTMP vs docetaxel

Condition

- Miscellaneous and site unspecified neoplasms benign
- Genitourinary tract disorders NEC

Synonym
prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: NKI;AVL

Intervention

Keyword: bone metastases, chemotherapy, prostate cancer, radionuclide

Outcome measures

Primary outcome

Pain relief / analgetics use at 6weeks

Secondary outcome

Number of patients that receive crossover treatment

Pain relief after crossover

Evaluation of toxicity related withdrawals

Study description

Background summary

Local radiotherapy, chemotherapy, and bisphosphonates were shown to provide some pain relief and bone seeking intravenous radionuclide treatment is an effective modality in these patients. Recently, docetaxel in a 3 weekly dosing of 75 mg/m2 was shown to result in pain relief in up to 35% of patients. Pain relief was experienced after the first two courses of docetaxel and pain relief was sustained but not increased after the 2 initial courses [5]. Moreover, a modest increase in overall survival was seen in patients receiving 3 weekly, but not weekly docetaxel in 2 large randomized trials. The side-effects of docetaxel chemotherapy prohibit its use in patients with a diminished hematopoietic function. Moreover, toxicities of the agent such as asthenia, nauseau and vomiting, and diarrhea led to withdrawal of treatment in 16% of the patients receiving a combination of docetaxel and mitoxantrone. Second line chemotherapy treatment with mitoxantrone after docetaxel was shown ineffective suggesting that alternative palliative options after chemotherapy are required.

Recently, samarium-153 bound to lexidronam-pentanatrium (153Sm-EDTMP) became available of radionuclide treatment of osseous metastases. The relatively short radiation half-life of 153Sm-EDTMP (2 days) render it an interesting agent with possibly less hematologic toxicity. 153Sm-EDTMP significantly reduced pain compared to placebo within 2 weeks with mild bone marrow suppression. Repeated dosing seemed feasible with clinically non-relevant changes in hematological parametes. These initial clinical studies with 153Sm-EDTMP suggest that it

provides a relatively non-toxic alternative to chemotherapeutic regimens such as docetaxel in patients with multiple osseous metastases.

Currently, several studies are evaluating the combined efficacy of radionuclide therapy and docetaxel chemotherapy. Although the radiosensitizing effects of docetaxel may potentiate efficacy, it may also increase toxicity in a population already at risk for hematological problems due to bone marrow suppression by osseous metastases. An important clinical question is the timing and order of applicating the palliative treatment modalities in metastasized prostate cancer. In the current study we want to evaluate the efficacy to obtain pain relief in patients with painful osseous metastases from prostate cancer for 3 weekly docetaxel and once 153Sm-EDTMP and evaluate possible success predicting factors to aid in the selection of patients for specific treatment sequelae.

Study objective

The sequential application of chemotherapy and radionuclide treatment in patients with symptomatic osseous metastasized prostate cancer. Patients with more than one painful osseous metastasis will be randomized between 153Sm-EDTMP or docetaxel 3 weekly 75mg/m2 (i.v.). Pain will be measured on a VAS of 10 points 3 times before treatment and again weekly until 6 weeks after start of treatment using a pain diary. A pain response is defined as a two-point reduction (20%) from baseline, without the need for palliative radiotherapy or change in pain medication. In case pain response is not obtained after two course of docetaxel or one dosing of 153Sm-EDTMP in the evaluation in week 5-6 patients receiving docetaxel will receive 153Sm-EDTMP or vice versa.

Study design

Patients with multiple osseous bone metastase from hormone refractory prostate cacner are eligible.

inclusion criteria:
1. more than one painful osseous metastasis from prostate cancer
2. bone metastases with uptake at pre-treatment bone scintigraphy
3. serum testosterone at castrate levels
4. WHO performance status 0-2
5. Adequate bone marrow function (ANC> 1.5 109/l, Thr > 100 109/l)
6. creatinine clearance > 60 ml/min
7. Adequate hepatic function (bilirubin <= 1.5 UNL , SGOT/AST <= 2.5 UNL and SGPT/ALT <= 2.5 UNL
8. Clinically normal cardiac function

exclusion criteria:
1. signs of myelumcompression due to spinal or epidural metastases.

2. earlier docetaxel chemotherapy for prostate cancer
3. earlier radionuclide treatment for prostate cancer
4. inability to sign informed consent or record VAS pain diary

After completion of VAS pain score and analgetic use documentation patients will be randomized between once 150 Mbq or docetaxel 75mg/m2 every 3 weeks. At 6weeks the pain score will be assessed and compared for both arms. Patients with insufficient pain relief will be offered the other treatment modality.

Intervention

group 1: docetaxel 75mg/m2 every 3 weeks
group 2: 150 MBq 153Sm-EDTMP once

Study burden and risks

1. docetaxel:
Hematological toxicity grade 3 and 4 is expected in the following percentages of patients and may be a reason to postpone docetaxel dosing: %
expected Grade 3 en 4
hematological toxicity:
- Anemia 5%
- Thrombocytopenia 1%
- Neutropenia 30-35%

Other toxicities observed in a comparable population were:
- alopecia 60-70%
- fatigue 50-55% (5% >grd2)
- nausea and vomiting 40-45%
- Diarrhea 30-35%
- Nail changes 30%
- Sensory neuropathy 30%
- Stomatitis 20%
- Peripheral edema 19%
- Changes in taste 18%
- Anorexia 17%
- Dyspnea 15%
- Myalgia 14%
- Tearing 10%
- Epistaxis 6%

In case of grade 3 and 4 toxicity it can be decided to postpone docetaxel dosing for one week dependent on severity and to reduce the dose as follows: if bilirubin/ASAT/ALAT or neutrophil count < 1.5 x10e9/L or platelet count < 100 x10e9/L delay dose one week; if grade IV hematotoxicity occurs (febrile neutropenia and thrombocytopenia) 25% dose reduction.

2. 153Sm-EDTMP:A decrease in hematological parameters may occur 3 to 5 weeks after radionuclide treatment. Hence, initial hematological parameters will be monitored before initiation of the study. For 153Sm-EDTMP the observed hematological toxicity consisted of a decrease of platelet count and white blood cell count during the 3-5 weeks period after treatment. No significant difference in grade 3 and 4 hematological toxicity was reported between placebo and 153Sm-EDTMP in a randomized study [15]. The hematological parameters, however, returned to normal by 6-8 weeks after treatment and no significant effect on serum hemoglobin was reported [15]. Hence, we do not anticipate hematological problems resulting in dose adaptations in the 153Sm-EDTMP. A possible second dosing of 153Sm-EDTMP or subsequent docetaxel treatment, however, should only be started after hematological changes due to the initial treatment have weaned off after 6-8 weeks. A small number of patients (7%) may report flare-up of pain several days after 153Sm-EDTMP administration [14]. This pain increase is over after several days and could always be managed with analgesics. Other side-effects such as diarrhea, vomiting, nausea asthenia, hypotension, peripheral edema, and headache have all been reported in comparable rates in the placebo arm of randomized studies and thus seem to be related to the stage of the disease the agent is given [14]. 153Sm-EDTMP is rapidly cleared from the blood by the kidneys. Thirty minutes after injection less than 10% of the initial dose was still presence in the plasma. After 4 and 24 hours after injection radioactivity in the plasma was reduced to 1,3 ± 0,7% and 0,05 ± 0,03% of the initial doses. Urine secretion occurred mainly in the first 4 hours after injection (30,3 ± 13,5%). After 12 hours 35,3 ± 13,6% of the administered dose was secreted through the urine. Studies on a group of 453 patiënts with a wide range of osseous lesions showed that 65,5 ± 15,5% of the total dose of 153Sm-EDTMP was bound to the skeleton.

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. more than one painful osseous metastasis from prostate cancer that can not be treated by external beam radiotherapy
2. bone metastases with uptake at pre-treatment bone scintigraphy
3. serum testosterone at castrate levels
4. WHO performance status 0-2
5. Adequate bone marrow function (ANC> 1.5 109/l, Thr > 100 109/l)
6. creatinine clearance > 60 ml/min
7. Adequate hepatic function (bilirubin <= 1.5 UNL , SGOT/AST <= 2.5 UNL and SGPT/ALT <= 2.5 UNL
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Exclusion criteria

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Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-03-2007
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Samarium [153Sm]-lexidronam-pentanatrium (QUADRAMET)
Product type:	Medicine
Brand name:	taxotere
Generic name:	docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-12-2006
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2006-006456-35-NL
CCMO	NL15395.031.06