Dexamethasone for the prevention of a pain flare after palliative radiotherapy for painful bone metastases: a multicenter double-blind placebo-controlled randomized study.

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Aim of the studyTo study the effectiveness and toxicity of dexamethasone to prevent the occurrence of a pain flare after short schedule radiotherapy for painful bone metastases and to define the optimal schedule of dosing.Research questions:1. What...

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

Summary

ID

NL-OMON44067

Source
ToetsingOnline

Brief title
Dexamethasone for pain flare after radiotherapy

Condition

- Skeletal neoplasms malignant and unspecified

Synonym
Bone metastases

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Bone metastases, Dexamethasone, Pain flare, Radiotherapy

Outcome measures

Primary outcome

The primary outcome measure of the study is the occurrence of a pain flare as defined by a two-point increase after radiotherapy of the worst pain score on an 11-point scale of 0 (no pain) to 10 (worst imaginable pain) compared to baseline without a decrease in analgesic intake, or a 25% increase in analgesic intake without decrease in worst pain score (according to international bone metastases consensus guidelines) (Chow 2007). Pain flare will be distinguished from progression of pain by requiring the worst pain score and analgesic intake to return to baseline levels after increase/flare (within 14 days of follow up).

Secondary outcome

Secondary outcomes are:

* pain scores (BPI) on days 1-14 and on day 28

* pain scales and quality of life (EORTC QLQ-BM22 and EORTC QLQ-PAL15) on days 7, 14 and 28

* side-effects of placebo and dexamethasone

Study description

Background summary

Patients with pain due to bone metastases are often treated with palliative short schedule external beam radiotherapy. Dependent on the institutional protocols, single fraction (8 Gy) or 5-6 fractions of 4 Gy are usually applied. Randomized studies have shown the equal effectiveness of both schedules in treating pain, with almost 70% of patients experiencing less or no pain within three to four weeks after treatment (Wu 2003). However, within 10 days after treatment a short term transient progression of pain may occur, the so-called pain flare (Chow 2005, Loblaw 2007, Hird 2009-1).
Two prospective observational studies reported patient-based daily pain scores after radiotherapy for painful bone metastases. Loblaw showed a pain flare in 44% patients after 8 Gy and in 24% patients after 20 Gy in 4 fractions (Loblaw 2007). The median duration of the pain flare was three days. A recent publication found no difference in pain flare in 111 patients after single vs. multiple fractions (39% vs. 41%, resp.) (Hird 2009-1). No data are available of the occurrence of pain flare in Dutch patients. The largest trial to date on painful bone metastases, the Dutch Bone Metastasis Study, was funded by OG and CKTO and randomized from 1996-1998 a total of 1157 patients between 8 Gy single fraction and 24 Gy in 6 fractions (PhD thesis, van der Linden 2005). Follow-up consisted of 12 weekly and thereafter monthly questionnaires on pain, pain medication and quality of life. In this study, daily scoring of pain to asses pain flare was not performed.
When a pain flare occurs oral dexamethasone can be prescribed. The rationale for administering steroids is to decrease edema that arises in the periostium of the affected bone shortly after radiotherapy and thereby to reduce pain (de Graeff 2006). Two small studies were performed to study the effectiveness of dexamethasone for treating a pain flare (Chow 2007, Hird 2009-2). Chow et al. administered 8 mg dexamethasone to 23 patients one hour before single fraction treatment and showed pain flare in only 24% of patients (95% CI 10-39%) within the first 10 days after radiotherapy (Chow 2007). Only one patient had a flare within two days after treatment. Dexamethasone was well tolerated. In a fase 2 study of the same research group 41 patients were administered 8 mg dexamethasone before and then for three consecutive days after single fraction treatment. They showed a pain flare in 22% of patients (with a median duration of one day), with 81% occurring within five days after treatment, and 95% within 10 days (Hird 2009-2). Both studies concluded that randomized studies are necessary to collect unbiased data on the occurrence and duration of pain flare and the effectiveness of drug treatment. Until now, no randomized studies were performed comparing dexamethasone with placebo or no treatment. The effectiveness of placebo vs. dexamethasone in the treatment of pain flare in patients after radiotherapy for painful bone metastases is the subject of this study.

Study objective

Aim of the study
To study the effectiveness and toxicity of dexamethasone to prevent the occurrence of a pain flare after short schedule radiotherapy for painful bone metastases and to define the optimal schedule of dosing.
Research questions:
1. What is the effectiveness of dexamethasone to prevent the occurrence of a pain flare after short schedule radiotherapy for painful bone metastases?
2. Is there a difference in effectiveness between a single dose of 8 mg dexamethasone before radiotherapy or a dose of 8 mg dexamethasone before radiotherapy in combination with three additional doses during the three following days?
3. What are the side effects of dexamethasone and placebo in patients treated with radiotherapy for painful bone metastases?
4. Does a pain flare predict for pain response to radiotherapy?

Study design

This study is a randomized, controlled, multicenter study in 411 patients with painful bone metastases who are referred for a short course of palliative radiotherapy. Short course radiotherapy encompasses all treatment schedules from one to six fractions of radiotherapy.
The study consists of three arms:
* Arm 1: day 0: placebo, day 1, 2 en 3: placebo
* Arm 2: day 0: 8 mg dexamethasone, day 1, 2 en 3: placebo
* Arm 3: day 0: 8 mg dexamethasone, day 1, 2 en 3: 8 mg dexamethasone
Day 0 is the first day of radiotherapy treatment. On day 0 the tablet of placebo or dexamethasone will be administered one hour before radiotherapy. On day 1, 2, and 3 the tablet of placebo or dexamethasone will be taken in the morning at about 8 a.m.

Intervention

Patients will be treated with dexamethasone and/or placebo orally during four days:
* Arm 1: day 0: placebo, day 1, 2 en 3: placebo
* Arm 2: day 0: 8 mg dexamethasone, day 1, 2 en 3: placebo
* Arm 3: day 0: 8 mg dexamethasone, day 1, 2 en 3: 8 mg dexamethasone
All patients will receive radiotherapy (1-6 fractions).

Study burden and risks

The burden and risks of the study are mainly related to the intake and side-effects of dexamethasone and placebo and to having to complete a questionnaire daily during 14 days and at day 28. Because of the short

duration of treatment with dexamethasone, only minor side effects (increased appetite, irritability and insomnia) are expected to occur. Study burden is expected to be low.
If oral administration of dexamethasone effectively reduces short-term pain flare in patients treated with palliative radiotherapy for painful bone metastases, it will be implemented into the daily practice of radiotherapy institutions throughout the Netherlands, resulting in decreased incidence and duration of pain flare after radiotherapy for painful bone metastases.

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

Patients with uncomplicated painful bone metastases, treated with 1-6 fractions of palliative radiotherapy

Pain intensity on a numeric rating scale of 2-8
Able to complete Dutch questionnaire

Exclusion criteria

Patients with hematological malignancies
Multiple sites to be irradiated
Previous radiotherapy for painful bone metastases
Current use of steroids or expected use within 2 weeks after radiotherapy
Life expectancy <8 weeks

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-01-2012
Enrollment:	294
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dexamethasone
Generic name:	dexamethasone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-11-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2013

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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-03-2013
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2013
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2014

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Application type:	Amendment
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2010-020174-42-NL
CCMO	NL32518.041.10