223Ra dichloride (Xofigo®)

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1. Introduction

More than 90% of patients with metastatic, castration-resistant prostate cancer have radiological evidence of bone metastases, which are a major cause of death, disability, decreased quality of life, and increased treatment cost among these patients.
^{223}Ra-dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range (<100 µm). As a bone-seeking calcimimetic, ^{223}Ra is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases. The high-energy alpha-particle radiation induces mainly double-stranded DNA breaks that result in a potent and highly localized cytotoxic effect in the targeted areas. The short path of the alpha particles also means that toxic effects on adjacent healthy tissue and particularly the bone marrow, may be minimized.
A phase 3 study showed that ^{223}Ra significantly prolonged overall survival in patients who had castration-resistant prostate cancer and bone metastases, with a 30% reduction in the risk of death, as compared to placebo. The median survival was longer among patients who received ^{223}Ra than among those who received placebo, the difference being 3,6 months. Reduction in pain was not an endpoint of the registration studies.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

^{223}Ra is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastases.

4. Side effects:

Bone marrow suppression

Bone marrow suppression, notably thrombocytopenia, neutropenia, leukopenia and pancytopenia, has been reported in patients treated with ^{223}Ra-dichloride. Therefore, haematological evaluation of patients must be performed at baseline and prior to every dose. Before the first administration, the absolute neutrophil count (ANC) should be ≥1,5 x 10^9/l, the platelet count ≥100 x 10^9/l and haemoglobin ≥10,0 g/dl. Before subsequent administrations, the ANC should be ≥1,0 x 10^9/l and the platelet count ≥50 x 10^9/l. If there is no improvement in these values within 6 weeks of the last administration of ^{223}Ra despite receiving the usual standard of care, further treatment with ^{223}Ra-dichloride should only be continued after a careful benefit/risk evaluation. Patients with evidence of compromised bone marrow reserve, e.g. following prior cytotoxic chemotherapy and/or radiation treatment (EBRT), or prostate cancer patients with advanced diffuse infiltration

of the bone ("superscan"), should be treated with caution. An increased incidence of haematological adverse reactions such as neutropenia and thrombocytopenia was observed in these patients during the phase III study.
The efficacy and safety of cytotoxic chemotherapy performed after treatment with ^{223}Ra has not been established. The limited data available indicates that patients who receive chemotherapy after ^{223}Ra-dichloride have a similar haematological profile as patients who receive chemotherapy after placebo.
Hoskin et al showed by a sub analysis of the ALSYMPCA trial that ^{223}Ra is also effective and well tolerated irrespective of previous docetaxel use.

Contraindications
Absolute contraindications are:
1. Platelet counts <100x10^9/l
2. Leucocyte levels <3,0x10^9/l
3. Continued breast-feeding
4. Pain in conjunction with a neurological deficit due to metastatic invasion: urgent local external beam radiotherapy is indicated in these cases
5. Pregnancy

5. Radiopharmaceutical
^{223}Ra-dichloride (Xofigo®)
a. Kinetics
After intravenous injection, ^{223}Ra is rapidly cleared from the blood and is incorporated primarily into bone and bone metastases, or excreted into the intestine. Fifteen minutes post injection, about 20% of the injected activity remains in the blood. At 4 h, about 4% of the injected activity remains in the blood, decreasing to less than 1% at 24 hafter the injection. The volume of distribution is higher than the blood volume indicating distribution to peripheral compartments. At 10 min post injection, activity is observed in the bone and in the intestine. The level of activity in the bone is in the range of 44% to 77% at 4 h post injection.
No significant uptake is seen in other organs such as heart, liver, kidneys, urinary bladder and spleen at 4 h post injection, faecal excretion is the major route of elimination from the body. About 5% is excreted in the urine and there is no evidence of hepatobiliary excretion. The whole body measurements at 7 days after injection (after correcting for decay) indicate that a median of 76% of the administered activity is excreted from the body. The rate of elimination of ^{223}Ra from the gastrointestinal tract is influenced by the high variability in intestinal transit rates across the population, with the normal range from once daily to once weekly bowel evacuation.
b. Dosage
The dose regimen of ^{223}Ra is an activity of 55 kBq per kg body weight, given at 4 week intervals for 6 injections.
c. Dosimetry
The absorbed radiation dose calculation was performed based on clinical bio-distribution data. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma

emitting radionuclides. For ^{223}Ra, primarily an alpha emitter, additional assumptions were made for the intestine, red marrow and bone/osteogenic cells, to provide the best possible absorbed dose calculations for Xofigo, considering its observed bio-distribution and specific characteristics.
There was no uptake of ^{223}Ra in most of the soft tissues observed, the alpha contribution to the total organ dose was set to zero for these organs. 2LLI: lower large intestine 3ULI: upper large intestine.

6. Method and after-care

^{223}Ra-dichloride is intended for intravenous administration. It must be administered by slow injection (generally up to 1 min). The intravenous access line or cannula must be flushed with isotonic saline for injection. Once ^{223}Ra has been correctly administered; there is no external dose rate from the patient. The product can be administered on an out-patient basis, and there are no restrictions on normal interactions with friends or relations.

7. Relation to other therapies

^{223}Ra-chloride is different to other bone seeking therapeutic radiopharmaceuticals, in that it is not indicated for treatment of pain from bone metastases. Approval of ^{223}Ra-dichloride was based on the improved survival in patients who received treatment. Pain was not an endpoint in the registration studies. In contrast to ^{188}Re-HEDP and ^{153}Sm-EDTMP, ^{223}Ra is not indicated for patient with bone metastases from other primaries than prostate cancer. External radiotherapy (or even neurosurgery) is always preferable in patients with myelumcompression or threatened/current neurological deficit. Extensive neurological examination should be a standard part of the analysis for patients with painful skeletal metastases. Previous external radiotherapy confined to a limited area is not a contraindication.

8. Literature

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