New radionuclides in metabolic therapy

*medical aspects*

Bieke Lambert  Nucleaire Geneeskunde  UZ Gent
X-ray tube

detector
History

1896  Henri Becquerel
1897  Pierre and Marie Curie ‘radio-activity’
1898  Pierre and Marie Curie ‘Radium-226’

1901  Radium-226 for skin tuberculosis
...Radium-226 and Radon-222 for treatment of skin lesions (1915)
...1930: glow in the dark
... Radium girls (1928)
History

1936 P32 as first systemic treatment for leukemia
1939 I131 treatment for Graves’ disease

1942 Sr89 for bone pain
1952 Radiosynovectomy

Dr. Hertz document on I131 for Graves’ disease
Present

Thyroid
- benign
- malignant

Neuro-endocrine tumours

Liver tumours
- primary
- metastasis

Bone metastasis

Arthritis

Brain tumorus and cysts

Lymphoma

Hematologic disorders

I-131

I-131 mIBG/ Radiolabelled somatostatine analogs

Sm-153 EDTMP/ Sr-89/Ra223

Radiolabelled colloids

Y-90 microspheres

Y-90 / I131 antibodies

P-32
In general

contra-indication for all RNT:
  pregnancy or inadequate contraception.

recent FANC/AFCN guidelines on a vigilant time window between the RNT and death
Samarium-153: 13d
Yttrium-90: 15 d for Zevalin, 30 d for other treatments
Sr89: 303 d
Ra223: 60 d
I131: 18 d (Thyroid Ca) and 29d (benign)
I131-mIBG: 47d
Radionuclide Treatment of benign thyroid disorders

Iodine-131
- beta emitter (E max 606 keV)
- gamma emitter (364 keV)
- $T_{1/2}$ 8 d

Patient preparation
- Stop Strumazol/PTU/iodine containing medication etc
- Assess volume, uptake (and kinetics)
- Calculate the activity
  - > 14 mCi hospital stay in radionuclide therapy ward
  - < 14 mCi ambulatory
Radionuclide Treatment of benign thyroid disorders

**Indications**

- Hyperthyroidism
  - Graves’ disease
  - Toxic adenoma
  - Toxic struma

- Volume reduction of euthyroid struma
131I treatment of benign thyroid disorders

- Low cost
- Effective
- Retreatment possible
- >> ambulatory

- Radioprotection
- Sialodenitis
- Evolution to hypothyroidism
- Excacerbation ophtalmopathy M Graves?
- Possibility of cancer induction
Treatment of Thyroid Cancer

- **Papillary**
  - Well differentiated
  - >> Iodine avid
  - Good prognosis

- **Follicular**
  - Very poorly differentiated
  - Not Iodine avid
  - >> FDG PET
  - Rare
  - Very bad prognosis

- **Anaplastic**
  - Neuroendocrine tumour
  - Rare
  - Octreotide scan

- **Medullar**
  - Rare
Differentiated Thyroid Cancer

- Papillary
- Follicular

Treatment of Thyroid Cancer

- Thyroidectomy
- Thyroxine substitution
- Suppress TSH stimulus
- I131
Role of I-123 scan?
- Simulates treatment with I-131
- Follow up
Follow up scan: normal findings
physiologic uptake in salivary glands, nasal and oral mucosa, stomach, intestines, bladder
Treatment of Thyroid Cancer

- Patient preparation:
  - provoke hypothyroidism/ TSH rise by withdrawing thyroid hormone substitution
  - recombinant TSH (Thyrogen) in order to avoid hypothyroidism
  - avoid exogenous iodine

- Always hospitalisation in radionuclide therapy ward and guidelines for radioprotection at home

- Post therapy scan
Radioprotection

- Stay in radionuclide therapy ward 24h-5 dd
- Radioprotective guidelines for 1-3 wks

Sleep separately
Toilet hygiene
Depending on job, stop working for several wks
No close (< 1m) contact for > 1h
...

Treatment of Thyroid Cancer
I\textsubscript{131} treatment most often used:

- Ablation of residual normal thyroid tissue post-resection
Besides treatment as adjuvant post thyroidectomy:

- Treatment of metastatic disease
Radiosynoviorthesis

Based on radiolabelled colloid

Radionuclide
Energy beta emission
~ size joint

Colloid particles 2-5µ
Phagocytosis
by synoviocytes and macrophages

Y-90
  t1/2 2.7 d
  Eβmax 2.3 MeV
  max range 11mm

Alternative P32

Re-186
  t1/2 3.7 d
  Eβmax 1.1 MeV
  max range 4mm

Er-169
  t1/2 9.4 d
  Eβmax 0.4 MeV
  max range 1mm
Indications ~ EANM guidelines

• Rheumatoid arthritis
• Spondylarthropathy (e.g. reactive or psoriatic arthritis)
• Other inflammatory joint diseases, e.g. Lyme disease, Behcet’s disease
• Persistent synovial effusion
• Haemophilic arthritis
• Calcium pyrophosphate dihydrate (CPPD) arthritis
• Pigmented villonodular synovitis (PVNS)
• Persistent effusion after joint prosthesis
• Undifferentiated arthritis (where the arthritis is characterised by synovitis, synovial thickening or effusion)
Radiosynoviorthesis

Contra-indications ~ EANM guidelines

1. Absolute
   - Pregnancy and breast-feeding
   - Local skin infection
   - Ruptured popliteal cyst (knee)

2. Relative
   - The radiopharmaceuticals should only be used in children and young patients (<20 years) if the benefit of treatment is likely to outweigh the potential hazards.
   - Extensive joint instability with bone destruction.
   - Evidence of significant cartilage loss within the joint.
Radiosynoviorthesis

Practical aspects

Intra-articular injection
except for knee, under fluoroscopic guidance
Immobilisation 48-72h
Interval between surgery/arthroscopy/punction: 2-6 wks

No major radioprotective issues
Less invasive than surgical synoviorthesis
Less revalidation needed than arthroscopic synoviorthesis
Longer lasting effect than IA steroids and possible to combine
Can be repeated if needed (>6mths)
No systemic side effects
Very safe in experienced hands
Practical aspects

Safety depends on expertise operator
Rare leakage/skin tatoes /necrosis
It takes time to respond
~15% pain and swelling 6-48h
Radiosynoviorthesis

**Efficacy**

depends on which joint and which underlying disease

>>> retrospective data: suggest good and long lasting responses

<<< prospective randomized trials
Efficacy

summary prospective randomized trials

Göbel et al. Rheumatol Int 2007
79 joints
Re186 alone vs Re186+steroid vs steroid alone
In favour of combined treatment: success rate 82% at 3 y
Less joint destruction?

44 pts, 68 joints
Er169/Re186+steroid vs steroid alone in upper extremity
69% response vs 32% at 12m

Jahangier et al. Arthritis Rheum 2005
97 pts, 50 knee joints, if 2 failed IA steroid injections in history
90Y +steroid vs steroid alone
Both groups only 48% response, no difference in response duration, negative effect
Y90 on joint destruction?
Liver Tumours

Radiopharmaceuticals for liver tumours such as radiolabelled Lipiodol or microspheres are delivered in the hepatic artery.
**Intra-arterial administration**

- Tumour >>>> Arteria hepatica
- Liver parenchyma 75% Vena Porta

Already a tumour selective effect by delivering the radionuclide in the hepatic artery (or even superselective in the feeding artery)

*No general anaesthesia needed*
How did it start?

Lipiodol

contrast material for the detection of HCC:

when injected into the hepatic artery
the oil is retained by HCCs for several weeks
to over a year, but it is cleared from
the normal liver parenchyma within 7 days

not suitable for systemic use
vehicle for anti-tumoral agents: chemo or Iodine-131
**131I-Lipiodol**

**Indications**

**Palliative setting**
Raoul et al. Hepatology 1997: Randomized trial 131I-Lip vs TACE

**Post-resection**

**While awaiting liver transplantation**
Brans et al. Cancer Biother Radiopharm 2001
Lambert et al. Cancer Biother Radiopharm 2005
131I-Lipiodol: Tolerance

Adverse events

Early
- moderate pyrexia (29%)
- hepatic pain on injection (12.5%)
- self limiting respiratory symptoms (3%)
- acute pneumonitis (0.5%-2%)
- transient decrease liver function (20%)

Late
- leukopenia (7%)
- lung fibrosis

Despite good tolerance, no escalation in activity possible due to radioprotection concerns

www.eanm.org
Yttrium-90 microspheres

non biodegradable particles loaded with Yttrium-90, that are trapped in the end arterioles following IA administration

\(^{90}\text{Y}\)-glass microspheres
- Therasphere, Nordion, Canada
- No randomized data available
- Mainly applied for HCC

\(^{90}\text{Y}\)-resin microspheres
- SIRspheres, Sirtex, Australia
- Some randomized data available
- Mainly applied for colorectal liver mets and HCC
Y-90 microspheres
Radioprotection Y-90 microspheres

\(^{90}\)Yttrium

- Pure beta-emitter
- 11 mm path length (max) soft tissue
- Shield with plastic, not with lead

No major radioprotective issues for the patients
No need for isolation/hospitalisation
Procedure / Patient preparation / MAA

$^{99m}$Tc MAA-scan
Procedure / Patient preparation / MAA

MAA-scan

SPECT/CT or fusion
Procedure / Post therapy scan

Tc99-MAA

90-Yttrium
Primary or secondary liver tumours

- HCC
- CRC
- mbreastCa, NET, CholangioCa, ....

- Karnofsky at least 70%
- (No ascites)
- Bilirubine < 2mg/dL (3 mg/dL if a single segment is treated)
- Child-Pugh not exceeding B7
- No or minimal extrahepatic disease
- (No prior radiotherapy of the abdomen)

Portal vein thrombosis is NOT a contra-indication
Yttrium-90 microspheres

Colorectal liver metastasis

Hendlisz et al. JCO 2010

N=46
Chemorefractory CRC liver mets

Cross over possible to combined therapy arm

Significant difference in TTLP and TTP
Colorectal liver metastasis

Future?

SIRFLOX/FOXFIRE study

FIRST LINE in CRC liver mets:

Randomized FOLFOX vs FOLFOX plus single session SIR-Spheres
Yttrium-90 microspheres

Barcelona Classification ‘BCLC’

Hepatocellular carcinoma

Very early stage (0)
Single <2 cm
Child-Pugh A, PS 0

Potential candidate for liver transplantation

No
Ablation

Yes
Portal pressure, bilirubin

Normal
Resection

Increased
Ablation

Early stage (A)
Single or 3 nodules <3 cm
Child-Pugh A-B, PS 0

Three nodules ≤3 cm
Associated diseases

No
Liver transplantation

Yes
Ablation

Intermediate stage (B)
Large multinodular
Child-Pugh A-B, PS 0

Advanced stage (C)
Portal invasion
Extrahepatic spread
Child-Pugh A-B, PS 1-2

Terminal stage (D)
Child-Pugh C
PS 3-4

Curative treatments

Palliative treatments

Forner, Bruix, Llovet. Lancet 2012
Yttrium-90 microspheres

Barcelona Classification ‘BCLC’

‘SIRT’ for intermediate stage HCC (not amenable to resection/RFA/Tx), especially if portal vein thrombosis is present
Yttrium-90 microspheres


“A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization.”

Cohort study comparing chemo-embolisation vs Yttrium-90 in 86 UNOS T3 HCC patients:
- more downstagings achieved with Yttrium-90
- better survival
- pitfall: different tumour biology?
Yttrium-90 microspheres

UZG results for downstaging HCC patients towards Tx

Downstaging in BCLC B and C patients

- remained outside Milan criteria for transplantation: 40%
- not assessable: 9%
- downstaged with radio-embolisation only: 46%
- downstaged with radio-embolisation and radiofrequent ablation: 6%
Yttrium-90 microspheres

Salem R. Gastroenterology 2009


Single center prospective longitudinal study
n= 291 HCC patients; 526 treatments
Toxicity
  Fatigue 57%, pain 23%, nausea/vomiting 20%, bilirubine gr III/IV 19%
Response
  WHO 42%, EASL 57%
TTP 8 m
Survival
Anti CD20 immunotherapy

Yttrium-90 labelled anti CD20 (Zevalin™)
Iodine-131 labelled anti CD20 (Bexxar™)
Anti CD20 immunotherapy

Yttrium-90 labelled anti CD20 (Zevalin™)

CD20 is an antigen is expressed in a relatively high quantity by some lymphomas.

Rituximab is a chimeric anti CD20 antibody. Rituximab as a cold antibody is an established anti tumour therapy.

Ibritumomab is the murine variant of the anti CD20 antibody, it can be labelled with In111 (imaging) or Y90 (therapy) by the chelating agent tiuxetan.
Anti CD20 immunotherapy

"Zevalin"

Indications

>>> Follicular or transformed low grade non Hodgkin lymphoma
Neuro-endocrine tumours

Somatostatin receptor overexpression

Octreotide as somatostin analogue
Various analogues ~ 5 receptor subtypes

Labelled with
Indium-111
Gallium-68
Yttrium-90
Lutheium-177

Ga68-DOTATOC PET UZ Leuven
Peptide Receptor Radionuclide Therapy (PRRT)

Radiolabelled somatostatin analogues

- Octreotide/Pentreotide (Indium-111)
- DOTATOC (Yttrium-90)
- DOTATATE (Lutetium-177)
- Lanreotide (Yttrium-90, Indium-111)
**Indications**

Inoperable tumours from neuro-endocrine origine

Tumours should have an uptake on pretherapy scan (OctreoScan, OctreoPET) that exceeds normal liver uptake.

>> GEP-NET

gastro-entero-pancreatic neuro-endocrine tumours overexpressing somatostatin subtype receptor 2 and 5

PRRT

Peptide Receptor Radionuclide Therapy

90Y-DOTATOC and Lu177-DOTATE

Efficacy
No RCTs available
>> symptomatic responses
15-35% radiological PR (limited CR)
Responses ~ long term outcome

Adverse events
For 90Y rare renal impairment (preventive amino acids infusions and dosimetry needed)
Haematologic adverse events ( >>>>mild)

International Neuroblastoma Staging System (INSS)
Meta-Iodo-Benzyl-Guanidine

Iodine-123 scan of neuroblastoma with massive bone marrow invasion
ml BG

Meta-Iodo-Benzyl-Guanidine

- Analogue of normetanephrine
- False neurotransmitter
- Radiolabelled with
  - Iodine-123 for imaging
  - staging neuroblastoma
  - diagnostic imaging of paraganglioma,
  - medullary thyroid cancer, NET, ...

Iodine-131 for therapy
Indications

Inoperable tumours from neuro-ectodermal origine

- Phaeochromocytoma / Paraganglioma
- Carcinoid tumours (if no avidity for somatostatin analogues)
- Medullary thyroid carcinoma (if no avidity for somatostatin analogues)
- Neuroblastoma
Pretherapy imaging assessment: diagnostic scan with I123-mIBG
- If tumour uptake > liver: therapy can be considered
- Some centers use a fixed activity of I131-mIBG for therapy (between 100-300mCi)
- Some centers estimate the activity of I131-mIBG for therapy based on 3 time point analysis of pretherapy scans. Aimed WB dose of 2 Gy.
I-131 mIBG

Practical aspects

- Administration of 131-mIBG
- Hospital stay radionuclide therapy ward for at least 72h and subsequent radioprotective guidelines
- Most activity is cleared renally within the first 5 days
- Post therapy scan
Use of I-131-MIBG therapy in case of neuroblastoma under investigation:

- High dose I-131-MIBG therapy as part of a myeloablative treatment
  Yanik et al. Journal of Clinical Oncology 2002; 20: 2142-2149

- Treatment of residual disease

- Combination with radiosensitizers and application of new radiosensitizers
Bone metastasis

Commonly available

- $^{89}\text{Sr-Cl}_2$
- $^{153}\text{Sm}$-lexidronam
- $^{186}\text{Re}$-etidronate

Research setting

- $^{188}\text{Re}$-HEDP
- $^{117m}\text{Sn}$-DTPA

EANM guidelines

$^{223}\text{Ra}$
## Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>half-life (days)</th>
<th>energy (MeV)</th>
<th>emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sr89-Cl</td>
<td>51</td>
<td>1.46</td>
<td>β</td>
</tr>
<tr>
<td>Sm153-EDTMP</td>
<td>1.9</td>
<td>0.71</td>
<td>β/γ</td>
</tr>
<tr>
<td>Re186-HEDP</td>
<td>3.8</td>
<td>1.07</td>
<td>β/γ</td>
</tr>
<tr>
<td>Re188-HEDP</td>
<td>0.7</td>
<td>2.02</td>
<td>β/γ</td>
</tr>
<tr>
<td>Sn117m-DTPA</td>
<td>13</td>
<td>CE</td>
<td>β/γ</td>
</tr>
</tbody>
</table>
Indications

< EANM guidelines for bone pain palliation

bone metastasis
- osteoblastic: shown on scintigraphy not only on plane X-ray
  - painful and multiple

Guidelines on a European, Belgian and Dutch level are not exclusively designed for prostate cancer patients. Most studies referred to also contain subsets of patients suffering breast cancer, lung cancer or bladder cancer.
Contra-Indications

< EANM guidelines for bone pain palliation

1. Absolute
   Pregnancy, breastfeeding

2. Relative
   - Hb < 90 g/l
   - total white cell count < 4.0 x 10⁹/l (Dutch: 3.0 x 10⁹/l)
   - platelets < 100 x 10⁹/l
   - rapidly deteriorating renal function – GFR < 30 ml/min
   - DIC: risk factor for severe thrombocytopenia
   - recent hemi-body external beam radiotherapy (3 m)
   - life expectancy of < 4 weeks. (Dutch: 12 weeks)

RNT has no place in the management of acute/chronic spinal cord compression or pathological fracture.
Patient preparation

- recent bone scintigraphy to confirm osteoblastic nature
- exclude other causes of increased uptake and pain (myelum compression)
- Lab test:
  - complete blood counts within 7 days prior to treatment (WBC > 3.0/4.0 x 10^9/l, platelets > 100 x 10^9/l)
  - exclude renal failure and DIC
- no recent other treatment with haematologic side effects
- Recent data suggest no interference of bisphosphonates
Practicalities

Administration and radioprotection

- slow IV infusion for Sr89, bolus injection for Sm153-EDTMP
- use perspex/lead shielding for vial and syringe
- single hospital visit (Sm153-EDTMP: 6 hours stay in Belgium): controlled area
- urine does contain radio-activity (place catheter in case of incontinence)
- FANC restrictions in case of early death post therapy
Practicalities

post therapy scan

\[ 99m \text{Tc-MDP} \]

\[ 153 \text{Sm-EDTMP} \]
Follow up

Toxicity

- “pain flare”: adapt medication for 2-10 days
- haematological:
  check blood week 3-8
  decrease in platelets and WBC
  nadir: about 4 weeks (Sm153), later for Sr89
  but not grade IV and not requiring treatment
  spontaneous recovery within 8-12 weeks
Efficacy

Sr89 (Metastron) vs placebo

Response due to the $^{89}\text{Sr}$ (150 MBq) was shown in small double-blind RCT.

1 study failed to show response compared to placebo, but: activity administered was probably too low: 3 x 75 MBq.

However: the RCTs comparing $^{89}\text{Sr}$ to placebo have weak methodology!

Finlay et al. Lancet Oncol 2005
Bauman et al. Radiother Oncol 2005
Efficacy

Sr89 (Metastron)

A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer

Aikaterini Dafermou\textsuperscript{1}, Paolo Colamussi\textsuperscript{1}, Melchiore Giganti\textsuperscript{1}, Corrado Cittanti\textsuperscript{1}, Maurizio Bestagno\textsuperscript{2}, Adriano Piffanelli\textsuperscript{1}

“Our results, in a total of 610 patients, all with prostate cancer and homogeneously evaluated, show that 60% of patients with diffuse skeletal metastases experience substantial pain relief or remain essentially pain-free (26%) for several months. If “mild” responses are also included, 81% of patients derive some benefit from the treatment….

Local radiotherapy has similar rates of success, but it is used only in patients with limited bone metastases and is not repeatable in the event of relapse of previously irradiated lesions.”

\textit{European Journal of Nuclear Medicine Vol. 28, No. 7, July 2001}
Sr89 (Metastron) vs EBRT

Oosterhof et al. Eur Urol 2003
- randomisation local field RT versus 150 MBq Sr89
- n=203 hormone-refractory prostate cancer
- equal response (35%)
- survival slightly but statistically significant better for local field RT
- cost $^{89}$Sr vs standard local field RT in the Netherlands: 25% higher for RNT!

Quilty et al. Radiother oncol 1994
- randomisation local field/hemibody RT versus 200 MBq Sr89
- n=305 hormone-refractory prostate cancer
- responses (66%) and survival equal
- *significant less new pain sites in case of $^{89}$Sr*
Porter et al. Semin Oncol 1993

- randomisation EBRT plus placebo versus EBRT plus 400 MBq $^{89}\text{Sr}$
- n=126 hormone-refractory prostate cancer
- significant more patients pain free and without analgetics at 3 m
- significant impact on daily activities
- less new pain sites, longer interval for next EBRT
Efficacy

Sm153-EDTMP (Quadramet)

Samarium Sm-153 Lexidronam for the Palliation of Bone Pain Associated with Metastases

- placebo versus 0.5 mCi/kg versus 1 mCi/kg group
- decline in VAS > placebo (p=0.034) at all weeks in 1 mCi/kg group
- decline in VAS > placebo (p=0.044) at week 1 in 0.5 mCi/kg group
- 1 mCi/kg group rapid onset of pain relief (< 1 week)
- pain relief up to 4 months after treatment
Efficacy

Sm153-EDTMP (Quadramet)

* P<.034 vs placebo
Repeated treatment with Sm153-EDTMP

Safety and Efficacy of Repeat Administration of Samarium Sm-153 Lexidronam to Patients With Metastatic Bone Pain

Sartor et al. Cancer 2007
Repeated treatment with Sm153-EDTMP

**FIGURE 2.** Mean pain scores at baseline, Week 4, and Week 8 after Dose 1, Dose 2, and Dose 3 of Sm-153.

Sartor et al. Cancer 2007
Issues requiring further research

To combine with chemotherapy?

Effects of Low-Dose Cisplatin on \( ^{89}\text{Sr} \) Therapy for Painful Bone Metastases from Prostate Cancer: A Randomized Clinical Trial

Rosa Sciuto, MD; Anna Festa, MD; Sandra Rea, MD; Rosella Pasqualoni, MD; Serenella Bergomi, MD; Germana Petrilli, MD; and Carlo L. Maini, MD  
*J Nucl Med* 2002; 43:79–86

- double blind RCT, \( n = 70 \), \( ^{89}\text{Sr} \)+cisplatinum vs \( ^{89}\text{Sr} \)+placebo
- significant better (62 vs 92%) and longer response (60 vs 120 d)
- comparable toxicity
Phase II Trial of Consolidation Docetaxel and Samarium-153 in Patients With Bone Metastases From Castration-Resistant Prostate Cancer

Karine Fizazi, Philippe Benzebou, Jean Lumbroso, Vincent Haddad, Christophe Massard, Marine Gross-Goupil, Mario Di Paola, Bernard Escudier, Christine Theodore, Yohann Leriot, Elodie Tourneux, Jeanne Bouzy, and Agnes Laplanche
Earlier use of RNT in the course of the disease?

“Can $^{89}$Sr delay the onset of bone pain?”

$^{89}$Sr: median time to development of pain of 213 days, with 33% free of pain at one year

Placebo: median time to development of pain of 168 days, with 18 % free of pain at one year. (p=0.01)

Issues requiring further research
Ra223
Ra223

Radium-223 decay chain
(predominant type of decay)

$^{223}\text{Ra}$
11.43 d
$\alpha$

$^{219}\text{Rn}$
3.96 s
$\alpha$

$^{215}\text{Po}$
1.78 ms
$\beta$

$^{211}\text{Bi}$
2.17 m
$\alpha$

$^{207}\text{Po}$
516 ms
$\beta$

$^{207}\text{Pb}$
stable
$\alpha$

$^{207}\text{Tl}$
4.77 m

**Ra223**

**AlphaRadin (Bayer Pharma AG)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>RaCl$_2$</td>
<td>Calcium mimetic, built in bone with high turn over</td>
</tr>
<tr>
<td>Radium-223</td>
<td>t1/2 11.4 d</td>
</tr>
<tr>
<td>Alpha emitter</td>
<td>high LET: very short path length, double strand breaks</td>
</tr>
</tbody>
</table>
Ra223

Alpha particle

Beta particle

Gamma radiation

Alpha particle

Beta particle

Gamma radiation

Paper

Aluminium

Concrete, lead or steel

www.vae.lt
Ra223

ALSYMPCA Study
Large RCT
6xRa223 over 6m vs placebo

HRPC
Min. 2 bone mets, no visceral mets
Symptomatic
Progressive PSA post docetaxel
or docetaxel refused

Less adverse events recorded in Ra223 group compared to placebo

# ALSYMPCA Adverse Events of Interest

## Hematologic

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th></th>
<th>Grades 3 or 4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Radium-223</td>
<td>Placebo (n = 253)</td>
<td>Radium-223 (n = 509)</td>
</tr>
<tr>
<td></td>
<td>(n = 509)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>136 (27)</td>
<td>69 (27)</td>
<td>54 (11)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20 (4)</td>
<td>2 (1)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>42 (8)</td>
<td>14 (6)</td>
<td>22 (4)</td>
</tr>
</tbody>
</table>
Ra223

MSKCC Radiation Safety Precautions for Clinical Phase I Study Following Alphradin, Radium-223, Injection

You will be given a card which informs people that you have received radioactive medicine, always carry this card with you.

There are NO restrictions regarding contact with other people after receiving the study drug.

During the first week after study drug injection there may be some radioactivity in your blood, urine, and stools, therefore you should take the following precautions:

- Use medical gloves when wiping up blood, urine, stools, or vomit, or when handling stained clothes.
- A normal toilet should be used in preference to a urinal. The sitting position should be used instead of the standing position.
- Wipe up any spilled urine or stool with a tissue and flush it away.
- If you are sick, wipe up spilled vomit with a tissue and flush it away.
- Ensure that you always thoroughly wash your hands after using the toilet or after wiping up spilled fluids.
- Wash any linen or clothes that become stained with urine, blood or stools separately from other clothes and rinse them thoroughly.
- If you are sexually active, the use of a condom is recommended during the first week after each study drug injection because there may be some slight radioactivity in the body fluids (but most in blood, urine and stools).
- If sampling of blood, urine or stools is necessary during the first week following study drug administration, please inform the personnel that you have been treated with radioactive Radium-223.
- If you need medical care such as an operation or hospital admission during the first week following administration, please inform the personnel that you have been treated with radioactive Radium-223.

Radiation Safety Considerations for the Use of 223RaCl2 DE in Men with Castration-resistant Prostate Cancer. Dauer, Lawrence et al.

DOI: 10.1097/HP.0b013e3182a82b37
Radiation Safety Considerations for the Use of 223RaCl2 DE in Men with Castration-resistant Prostate Cancer. Dauer, Lawrence et al.

DOI: 10.1097/HP.0b013e3182a82b37