Where Do We See Alpha Emitters in Clinical Practice? A Radiation Oncology Perspective

Joe M. O’Sullivan
Professor of Radiation Oncology
Queen’s University Belfast
Consultant Oncologist
Northern Ireland Cancer Centre, Belfast
Co-Director
FASTMAN Centre of Excellence for Prostate Cancer Research
COI #1

- Advisory board + Speakers’ bureau: Astellas, Bayer, Janssen, Sanofi
- Research funding (Institution): Bayer
COI #2 - I Love the Rays!
Gentlemen, these rays will be very important in treating prostate cancer...
Predicted trends in prostate cancer mortality

Data: Cancer Research UK

40% Reduction in Prostate Cancer Death in past 15 years
Prostate Cancer mortality by age at death (UK)

Large majority of deaths occur over 75y

Data: Cancer Research UK
What is driving the better outcomes in prostate cancer mortality?

Probably not Surgery
Radiation + Androgen Deprivation Therapy in locally advanced prostate cancer

Actual lives saved!
Can local radiotherapy influence outcomes in metastatic prostate cancer? STAMPEDE Arm H - Study design

**Men with newly diagnosed metastatic prostate cancer**

ADT +/- docetaxel (SOC) 1:1 ADT +/- docetaxel (SOC) + prostate radiotherapy

36Gy/6 fractions/6 weeks or 55Gy/20 fractions/4 weeks

Schedule nominated before randomisation

**Stratification variable**
(<70 vs ≥70 years), nodal involvement (N0 vs N1 vs Nx), randomising site, WHO performance status (0 vs 1 or 2), type of ADT, aspirin or NSAID use, docetaxel use
Radiotherapy to the prostate in metastatic disease setting
- Results of STAMPEDE Arm H

Low burden

Radiation - Improving survival in (low volume) metastatic castration sensitive prostate cancer

Metastatic Castration Resistant Prostate Cancer (mCRPC)

- Average of 12 months response to Androgen Deprivation Therapy (ADT)
- Biochemical progression usually first indication of resistance
- Metastatic CRPC is an incurable condition - median survival in modern era - 22 months

Clarke et al, J Clin Oncol 31, 2013 (suppl; abstr 5012)
Targeting bone metastases really matters in metastatic castration resistant prostate cancer (mCRPC)

• ~90% of patients with CRPC have bone metastases

• Bone metastases are the main cause of death in CRPC

• Symptomatic Skeletal Events (SSEs)
  – Major impact on QoL
The phenotype of prostate cancer in bone facilitates **imaging** and therapy

Images courtesy of Noel Clarke
The phenotype of prostate cancer in bone facilitates imaging and **therapy**

- **EDTMP**, ethylenediamine tetra(methylene phosphonic acid); **HEDP**, hydroxyethylidene diphosphonate

Images courtesy Chris Parker

- **99mTc MDP**
- **223RaCl₂**

**Delivery of radioactive payload to metastases**

EDTMP, ethylenediamine tetra(methylene phosphonic acid); HEDP, hydroxyethylidene diphosphonate
Molecular Radiotherapy for bone metastases
Molecular Radiotherapy for bone metastases

Molecular Radiotherapy

Alpha-emitters  Beta-emitters
### Single agent beta-emitting radionuclides: Published RCTs

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Tumour</th>
<th>Study design</th>
<th>Pain response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porter (1993)</td>
<td>126</td>
<td>Prostate</td>
<td>XRT plus Sr-89 vs XRT plus placebo</td>
<td>CR 30-60%; longer time to new pain in Sr-89 patients</td>
</tr>
<tr>
<td>Oosterhof (2003)</td>
<td>203</td>
<td>Prostate</td>
<td>Sr-89 vs local XRT</td>
<td>CR ~35%</td>
</tr>
<tr>
<td>Quilty (1994)</td>
<td>284</td>
<td>Prostate</td>
<td>Sr-89 vs local XRT or HBI</td>
<td>PR 65%, Significantly less new pain sites</td>
</tr>
<tr>
<td>Buchali (1988)</td>
<td>49</td>
<td>Prostate</td>
<td>Sr-89 vs placebo</td>
<td>CR 37%</td>
</tr>
<tr>
<td>Lewington (1991)</td>
<td>32</td>
<td>Prostate</td>
<td>Sr-89 vs placebo (plus Sr-88)</td>
<td>CR 38%</td>
</tr>
<tr>
<td>Serafini (1998)</td>
<td>118</td>
<td>Breast + prostate*</td>
<td>Sm-153 37 vs 18.5 MBq/kg vs placebo</td>
<td>PR 70%; CR 31%</td>
</tr>
<tr>
<td>Sartor (2004)</td>
<td>114</td>
<td>Breast + prostate*</td>
<td>Sm-153 37 vs 18.5 MBq/kg</td>
<td>PR 70%</td>
</tr>
<tr>
<td>Tian (1999)</td>
<td>105</td>
<td>Breast + prostate*</td>
<td>Sm-153 37 vs 18.5 MBq/kg</td>
<td>PR 83%</td>
</tr>
<tr>
<td>Resche (1997)</td>
<td>114</td>
<td>Breast + prostate*</td>
<td>Sm-153 37 vs 18.5 MBq/kg</td>
<td>PR 70%</td>
</tr>
<tr>
<td>Han (2002)</td>
<td>111</td>
<td>Prostate</td>
<td>Re-186 1295-2960 MBq vs placebo</td>
<td>PR 65%</td>
</tr>
</tbody>
</table>

**Small trials**

- Pain response rates ~ 40-60%
- Dose limiting toxicity ~ haematological
- No survival benefit demonstrated

---

What makes targeted alpha therapy different?

<table>
<thead>
<tr>
<th>Alpha emitter</th>
<th>Beta emitter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Overall survival(^1)</td>
</tr>
<tr>
<td><strong>Approved therapies</strong></td>
<td>Radium-223</td>
</tr>
<tr>
<td></td>
<td>Samarium-153</td>
</tr>
<tr>
<td><strong>Dosage</strong> (kBq/kg)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Particle size</strong> (μm)</td>
<td>50–80</td>
</tr>
<tr>
<td><strong>LET (keV/μm)</strong></td>
<td>~100</td>
</tr>
<tr>
<td><strong>Particle range in cell diameters</strong></td>
<td>2–10</td>
</tr>
<tr>
<td><strong>Type of DNA damage</strong></td>
<td>Double-strand breaks (lethal, more difficult to repair)</td>
</tr>
</tbody>
</table>

Radium-223
Targeted Alpha Therapy with Dual Mode of Action


Biology Contribution

Mechanistic Modeling of Radium-223 Treatment of Bone Metastases

Hugo M.R. Moreira, MSc,⇑ Francisco D.C. Guerra Liberal, MSc,⇑ Joe M. O’Sullivan, FRR(RCSI),⇑ Stephen J. McMahon, PhD,⇑ and Kevin M. Prise, PhD

*Centre for Cancer Research & Cell Biology, Queen’s University Belfast, Belfast, Northern Ireland, United Kingdom; †Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Esferica, Portugal; and Clinical Oncology, Northern Ireland Cancer Centre, Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom

Received Mar 31, 2018. Accepted for publication Dec 6, 2018.

Summary

Purpose: Despite the effectiveness of 223RaCl2 for treating patients with symptomatic bone metastatic disease, its mechanisms of action are still unclear. Even established dosimetric approaches differ considerably in their conclusions. In silico tumor models bring a new perspective to this situation because they can quantitatively simulate the interaction of α-particles with the target(s). Here, we investigated 3 different mathematical models of tumor growth that consider the radiation effect of radium-223 (223Ra) treatments and compared the results with clinical data.

Methods and Materials: The well-established Gompertz growth model was applied to simulate metastatic tumor burden. On the basis of published measurements of 223Ra uptake, we have incorporated the radiation effect of α-particles into the model and compared the median survival of the 3 different radium-223 (223Ra) dosimetric models among patients with metastatic bone disease.

Keywords: Radium-223; Tumor growth; Mathematical modeling; Dosimetry; Cancer treatment

Abstract

Radium-223 - Modeling
Phase 3 ALSYMPCA: trial design

**Primary endpoint:** Overall survival

**Secondary endpoints:** time to first SRE, time to total ALP progression, total ALP response, total ALP normalization, time to PSA progression, safety, and QoL

**TREATMENT PHASE**
Six injections at 4-week intervals

- Radium 223 + best standard of care
- Placebo + best standard of care

**FOLLOW-UP PHASE**

- **Stratification factors**
  - Total ALP <220 U/L vs ≥220 U/L
  - Bisphosphonate use (yes vs no)
  - Prior docetaxel (yes vs no)

- **Key inclusion criteria**
  - Confirmed symptomatic CRPC
  - ≥2 bone metastases
  - No known visceral metastases
  - Post-docetaxel or unfit for docetaxel

**Assessments**

0  6  8  10  12  16  20  24  28  32  36

Month

N=921 mCRPC

Randomization 2:1
Phase 3 ALSYMPCA: overall survival

Median OS, months
- Radium 223: 14.9
- Placebo: 11.3

HR
- Radium 223: 0.70
- Placebo: 0.70

95% CI
- Radium 223: 0.58–0.83
- Placebo: 0.58–0.83

p value
- Radium 223: <0.001
- Placebo: <0.001

Median OS Δ: 3.6 months
Phase 3 ALSYMPCA: time to first SSE

<table>
<thead>
<tr>
<th></th>
<th>Radium 223 (n=614)</th>
<th>Placebo (n=307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first SSE, months</td>
<td>15.6</td>
<td>9.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.52–0.83</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

ERA 223: Concomitant Treatment of Asymptomatic or Mildly Symptomatic CRPC with Bone Metastases with Radium-223 in Combination with Abiraterone and Prednisone

**Study Population**
- Patients with bone-predominant mCRPC
- Asymptomatic or mildly symptomatic
- ≥2 bone metastases
- ECOG PS of 0 or 1
- No known brain or visceral metastases

**Endpoints**
- Primary endpoint: SSE-FS
- Secondary endpoints:
  - Overall survival
  - Time to opiate use for cancer pain
  - Time to pain progression
  - Time to chemotherapy
  - Radiologic PFS
  - Safety

**Stratification factors**
- Geographical region
- Use of bone health agents
- ALP level at baseline (ALP <90 vs ≥90 U/L)

**Randomization**
1:1

**N=806**

Radium-223 dichloride 55 kBq/kg IV every 4 weeks for 6 cycles
In combination with abiraterone (1000 mg qd) + prednisone/prednisolone (5 mg bid)

Matching placebo
In combination with abiraterone (1000 mg/qd) + prednisone/prednisolone (5 mg/bid)

**Notes:**
- ERA 223 was unblinded early on November 17, 2017, based on the recommendation of the IDMC
- The current results are based on this early analysis after unblinding
- The last event to conduct the primary analysis occurred on February 15, 2018. The study is still ongoing for follow up
Increased SSE-FS Events and Decreased Rate of Survival Were Observed in the Combination Arm (Interim Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 + abiraterone + prednisone</th>
<th>Placebo + abiraterone + prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSE-FS events, no. patients with event</td>
<td>43.4% (174/401)</td>
<td>39.8% (161/405)</td>
</tr>
<tr>
<td>Median (95% CIs) SSE-FS, months</td>
<td>22.6 (20.4, 29.3)</td>
<td>28.7 (21.8, 31.6)</td>
</tr>
</tbody>
</table>

**Survival analysis**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>34.7% (139/401)</td>
<td>27.4% (111/405)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>HR (95% CIs)</td>
<td>1.347 (1.047, 1.732)</td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CIs), months</td>
<td>30.7 (25.2, 35.6)</td>
<td>33.3 (30.2, A)</td>
</tr>
</tbody>
</table>

**Fractures**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 fracture</td>
<td>26.0% (102/392)</td>
<td>8.1% (32/394)</td>
</tr>
</tbody>
</table>

A, value cannot be estimated due to censored data.

Unplanned interim analysis: data cutoff November 24, 2017.
CI, confidence interval; HR, hazard ratio; OS, overall survival; SSE-FS, symptomatic skeletal event-free survival.
ERA-223: Overall Survival (Primary Analysis)

Risk of fracture mitigated by bone health agent

Ongoing RCT Ra-223 + Enzalutamide
Potential role for Radium-223 in mCSPC
ADRRAD Trial (Belfast)

- Phase 1/2
- T1-4 N0-1 M1b

Primary Endpoints
- Toxicity
- Quality of Life

Secondary end points
- WBMRI response
- PSA/ALP
- CTCs

Docetaxel x 6

Androgen Deprivation Therapy

74Gy/60 37fr prostate + Nodes (VMAT)

30/30 patients now recruited
No unexpected toxicity
No dose limiting toxicity
ADRRAD patient # 1

At diagnosis
PSA 3300ng/ml
ALP 2000

Post ADT + 6 x Docetaxel
PSA 24ng/ml
ALP 180

Post RT + 6 x Radium-223
PSA <0.03ng/ml
ALP 70
STAMPEDE – next steps – More Radiotherapy!

- Standard-of-care (SOC) = ADT (+/RT)
- SOC+zoledronic acid
- SOC+docetaxel
- SOC+celecoxib
- SOC+zoledronic acid+docetaxel
- SOC+zoledronic acid+celecoxib
- SOC+Abi
- SOC+M1RT (M1)
- SOC+Enzalutamide
- SOC+Enzalutamide+Abiraterone
- SOC+Rucaparib
- SOC + SABR to Oligomet (low volume)

- Pts in comparison
- A Pts not in comparison
- Abiraterone
- # SOC+Enzalutamide+Abiraterone
Conclusions 1

- Ionising radiation has key disease modifying roles at multiple points in prostate cancer natural history
  - Improved survival/cure in locally advanced disease (*EBRT +/- ADT +/- Abiraterone/Docetaxel*)
  - Improved survival in ‘low volume’ metastases (*EBRT to prostate*)
  - Improved survival in lethal prostate cancer (*Radium-223*)

- Potential role of IR in prostate cancer
  - Oligometastatic disease (*SABR + Abiraterone/Docetaxel*)
  - mCSPC in bone (*EBRT + Docetaxel/Abiraterone + Radium-223*)
  - mCRPC/mCSPC (*PSMA targeted radionuclide therapy Lu-177, Th-227, Ac-225*)
Conclusions 2

- **Modeling**
  - Need to better understand the MoA of Radium-223
- **Precision medicine**
  - DNA repair defects
- **Targeted Alpha Therapy Dosimetry**
  - Huge potential to optimise therapy
  - Challenges for Radium-223 dosimetry
  - Essential for PSMA targeted therapy
- **Targeted Alpha Therapy Combination therapy**
  - Evidence of increased fracture risk for Radium-223 + Abiraterone-emphasises importance of large RCTs
  - Potential for combination with immunotherapy
  - Radionuclide cocktails