Radium Revisited

Targeting of skeletal metastases by the alpha-emitter Radium-223

Roy H. Larsen and Øyvind S. Bruland

The morbidity associated with cancer affecting the skeleton is serious. Pain, pathological fractures, as well as hypercalcemia and bone marrow insufficiency have a devastating impact on the patients' quality of life. In particular metastases in the vertebrae leading to spinal cord compression may be disastrous.

External radiotherapy is widely used to relieve pain from skeletal metastases, but its lack of selectivity limits its usefulness. Normal cells within the target volume receive the same radiation dose, as do the tumour cells. Since the radiosensitivity of the latter usually is not much higher than that of the normal cells, the therapeutic index is generally low. The use of wide-field external irradiation in patients with widespread skeletal metastases is limited by its acute toxicity and the subsequent bone marrow suppression.

In contrast, preferential destruction of cancer cells at multiple sites can be accomplished by targeted radionuclide therapy, in which a bone-seeking radiopharamaceutical is injected intravenously.

This paper reviews our recent experiments with ^{223}Ra in the management of patients with bone metastases. Furthermore, it outlines the rationale for the use of alpha-emitters. Our work has led to a patented product which now is under clinical development with the trademark Alpharadin^{R} (see information at www.algeta.com)

Radium – some historical remarks

The discovery of radium (L. Radius, ray) by Marie and Pierre Curie in 1898, represents a unique chapter in the history of natural sciences and opened a new era in the treatment of cancer (1-3). The elemental form was isolated in 1911 by electrolysis of a solution of pure radium chloride, employing a mercury cathode. After distillation in an atmosphere of hydrogen this amalgam yielded the pure metal.

Originally, radium was obtained from the rich pitchblende ore found in Joachimsthal, Bohemia, with approximately 1 g of radium in 7 tons of mineral. Radium is the heaviest of the earth alkaline elements (4-6). All isotopes of radium are radioactive of which ^{226}Ra has the longest half-life ($t_{1/2}$ =1600 years). Radium-226 is the most abundant radium isotope in nature and is formed in the decay chain from ^{238}U. Other naturally occurring radium isotopes are ^{228}Ra and ^{224}Ra from the ^{232}Th-family and ^{223}Ra from the ^{235}U-family. One gram of ^{226}Ra undergoes 3.7×10^{10} disintegrations per s, a number defining the unit Curie. In its decay this amount produces about 0.0001 ml radon gas per day.

Radium has been used in the production of self-luminous paints, neutron sources, and in medicine for the treatment of a number of diseases (7-9). In the first third of last century radium was used extensively in medical practice. In fact, at a time it was considered a universal remedy (1, 8). For many years radium-226 was considered the gold standard in gynecological brachytherapy and it was not until recently that it is being replaced in most hospitals by other sources with more advantageous properties and aspects related to radiation protection.

An important question is to what extent radium is carcinogenic. It is well known that

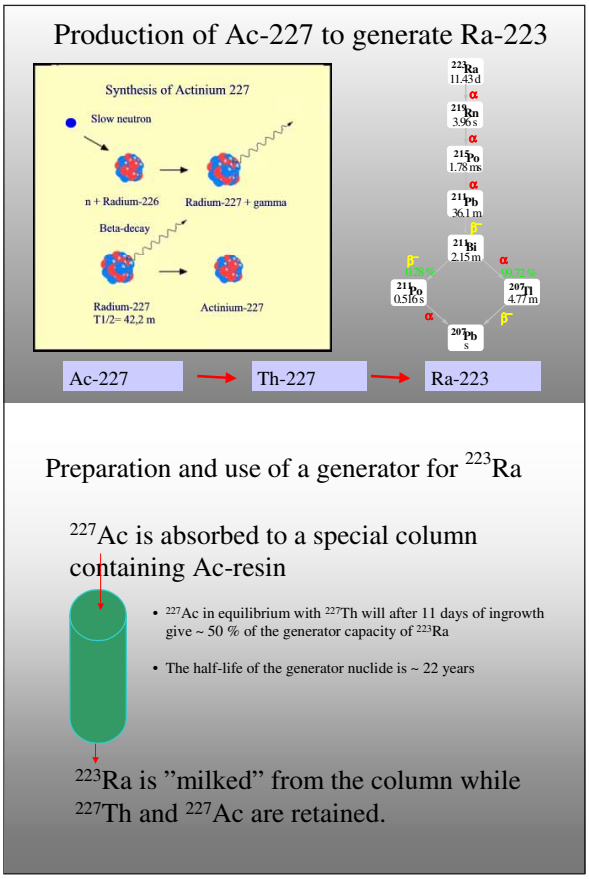

***Fig 1 A&B** Production/Deacay scheme & Generator*

bone cancer may occur in subjects exposed to ^{226}Ra (10,11). However, at intermediate dose levels (below 20 Gy to the bone for ^{226}Ra) no significant increase in cancer was observed in humans.

For several decades injections of ^{224}Ra ($t_{1/2}$ = 3.2 days) was used to treat ankylosing spondylitits (12). It has recently been reintroduced and reapproved for this indication in Germany (13). In the case of ^{224}Ra, long term follow up of patients receiving moderate levels revealed no significant difference in overall cancer incidence or life expectancy compared to a control population (14).

Radiochemical properties of Radium-223

Radium-223 is in our view the most promising one of the radium isotopes with favourable features for use in targeted radiotherapy. It decays ($t_{1/2}$ = 11.4 days) via a chain of short-lived daughter nuclides to stable lead, producing four alpha particles. In the decay of ^{223}Ra, the fraction of energy emitted as α-particles is ~ 96%. Importantly, the noble gas daughter nuclide ^{219}Rn has a half-life of less than 4 seconds, in contrast to the long-lived radon-daughters from the other radium isotopes.

Radium-223 can be produced in large amounts and relatively inexpensively. Sources of the precursor ^{227}Ac ($t_{1/2}$ = 21.7 y) can be used as a long-term operating generator for ^{223}Ra (15). Actinium-227 can be produced by neutron irradiation of the relatively commonly available ^{226}Ra. Moreover, ^{223}Ra's half-life provides sufficient time for its preparation, distribution, including long distance shipment, and administration to patients. Its low gamma-irradiation is favourable for the point of view of handling, radiation protection and treatment on an out patient basis. A novel ^{223}Ra-based radiopharmaceutical, named Alpharadin^{R}, is currently under clinical testing (see below).

The α-particles from the first three nuclides in the decay chain are emitted almost instantaneously (Figure 1). They are therefore likely to contribute to the radiation dose in the vicinity of the site of ^{223}Ra decay. Hence, ^{223}Ra has the potential to deliver a therapeutically relevant tumour dose from a relatively small amount of administered activity without causing unacceptable doses to non-target tissue.

Significant efforts have been made to conjugate ^{223}Ra to a tumor seeking carrier

molecule, e.g, monoclonal antibody. Radioimmune-conjugates of metallic radionuclides require that the metal is bound to the protein via a bifunctional chelator (16). For antibody-based tumour targeting of ^{223}Ra, redistribution of daughter nuclides may occur due to diffusion of its noble gas daughter ^{219}Rn, and the recoil during disintegration. Hence, a highly stable and inert chelate is required for most applications of conjugates based on ^{223}Ra.

Bone-seeking radiopharmaceuticals

Internal radioisotope therapy, sometimes called metabolic radiotherapy, involves a dynamic interaction between three players: the target proper, the effector moiety and the bone-targeting vehicle. Bone-seeking radiopharmaceuticals may be used to selectively deliver ionising radiation to skeletal metastases, largely to areas of increased osteoblastic activity. As mentioned above this form of treatment will target multiple metastases simultaneously; symptomatic as well as asymptomatic foci.

The target in bony tissue is particularly osteoblastic sites and areas of new bone formation. The osteoid and woven bone strongly accumulate the radiopharmaceutical as they adhere to and form complexes with the newly made hydroxy-apatite framework. In the case of breast cancer, it is believed that the radiopharmaceuticals become concentrated predominantly in the reactive layer of proliferating osteoblasts surrounding the metastases, whereas in prostate cancer the metastases usually consist of a network where the tumour cells are embedded in primitive bony matrix.

Currently, two principal classes of therapeutic bone-seeking radiopharmaceuticals are available: *Calcium analogues* and *Phosphonates*. In the commercially available formulations the radioactive isotopes involved are beta-emitters, viz. ^{89}Sr and ^{153}Sm. Metastron^{R} (Nycomed-Amerham) is approved in the US as well as in most European countries, and recently ^{153}Sm-EDTMP Quadramet/Lexidronam^{R} (Schering AG/Berlex) has also reached the market.

Patients may benefit from a single intravenous infusion, with pain relief which may occur within the first weeks and may last for several months. Clinical phase-II studies with ^{89}Sr have shown effective palliation of pain in a majority of patients with metastatic prostate cancer. Initial reports demonstrate palliative responses in up to 75% of the patients, with as many as 25% being able to stop taking analgesics (17-19). Double blind studies have compared radioactive and stable strontium and confirmed the therapeutic effect of Metastron. Effective pain palliation was, however, observed in a lower percentage of the patients than reported in the phase-II trials (20,21). Some claim that Metastron is as effective as external radiotherapy and that the onset of pain at new sites may be delayed (22). Authors have attempted to document a dose-response relationship with Metastron, but both failed to do so (23).

Radiation doses following i.v. Metastron injections (physical half-life of 50.5 days) indicate a fairly low dose deposition at the index sites (24,25). Absorbed doses in the range of 20 - 40 Gy, deposited as a continuously declining dose-rate during 16 weeks to one year, were reported. This low dose-rate suggests a questionable tumouricidal effect.

Quadramet/Lexidronam^{R} mentioned above has a shorter physical half-life of 46.3 h. The higher dose-rate, and the shorter range of its less energetic electrons may improve its therapeutic index compared to that of Metastron (26-29). To our knowledge, however, no comparative studies have been reported.

Although repeated injections of ^{153}Sm-EDTMP are permissible, bone marrow toxicity, often with delayed and unpredictable recovery, generally limits the therapeutic usefulness of beta-emitting radiopharmaceuticals.

Radio- and tumourbiological aspects of skeletal metastases

As mentioned above, previous clinical therapeutic studies in patients with skeletal metastases have utilised beta-emitting radionuclides as the effector arm. Electrons are light, sparsely ionising particles (low LET), have a low radiobiological effect and a track length in tissue up to a few mm. In contrast, alpha particles are heavy (Helium nuclei with two positive charges) and densely ionising (high LET). Hence, they yield a massive deposition of energy per unit track length and have a short range of less that 100 µm. Alpha particles induce non-reparable double DNA-strand brakes. This may be important as patients with skeletal metastases often have chemoresistant disease. Also micrometastases with dormant clonogenic tumour cells residing in G_0 may be eliminated by high-LET irradiation from alpha emitters (30).

Bone metastases are usually caused by hematogenous spread of malignant cells. Most skeletal metastases are probably derived from clonogenic tumour cells, seeded via the blood stream and arrested in the red bone marrow sinusoids, i.e. in compartments within the axial skeleton. There is firm experimental evidence that initially such tumour cells attach themselves primarily to the endosteal bony surface, and that the interphase between bone and red bone-marrow constitutes a favourable microenvironment for tumour cell proliferation. It is now appreciated that the release of bone derived growth factors and cytokines from bone in the process of being resorbed, can both attract cancer cells to the bony surfaces and facilitate their growth. Thus the "seed and soil hypothesis", originally launched by Paget (31), has received renewed attention (32).

An intriguing possibility is that clonogenic tumour cells may reside at the interface between bone and bone marrow as "in transit" micrometastases that proliferate and mature by means of the favourable soil provided. Mutations and chromosomal re-arrangements may accumulate, resulting in cells with increased metastatic potential, for secondary spread to visceral organs such as lungs and liver.

With α-emitters the endosteal bone surface receives a very high radiation dose at the same time as a significant fraction of the marrow is spared, thereby increasing the survival of marrow cells (33-36). In particular ^{223}Ra, together with its daughter nuclides, may deliver an intense and highly localised field of radiation to the bone surfaces with significantly less bone marrow dose compared to the currently used electron emitting bone seekers (37).

Alpharadin^{R}: Pre-clinical studies

In a recent study we explored the bone seeking properties of ^{223}Ra and compared it to that of the ß-emitter ^{89}Sr (37). The biodistributions of the two radionuclides were studied in mice by determining their tissue content of radioactivity at various time-points after intravenous administration. Dosimetry calculations were performed for soft tissues and bone. In addition, doses were estimated for bone marrow containing cavities assuming spherical configurations (38).

It was found that both radionuclides were concentrated more in bone than in soft tissues. The measured uptake of ^{223}Ra was the highest in bone. After 24 hours the femur content of ^{223}Ra was 40.1 ± 7.7 % of ID/g, while ^{223}Ra was rapidly cleared from the soft tissues within the first 24 hours. The bone uptake increased with time up to 24 h. Furthermore, there was almost no redistribution of daughter nuclides from bone. Thus it was determined to be about 2 % at 6 h and was not detectable (less than 1 %) at 3 days. Finally, estimates of dose deposition in bone-marrow demonstrated that an important advantage of using alpha particle emitters is to spare bone-marrow (37).

The therapeutic efficacy of ^{223}Ra was then studied in a nude rat model (39). Animals injected with 10^6 MT-1 human breast cancer

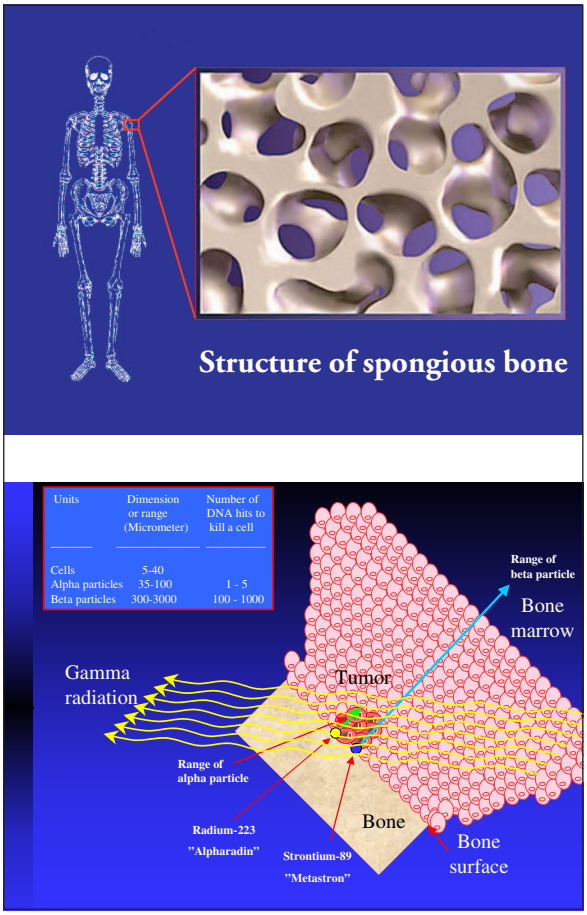

Fig 2 A&B. Schematic representation of spongious bone, red bone-marrow & track-length

cells into the left ventricle, were treated seven days later with ^{223}Ra-doses in the range 6-30 kBq. All untreated control animals had to be sacrificed due to tumour induced paralysis 20-30 days following injection with tumour cells, whereas the rats treated with ≥ 10 kBq of ^{223}Ra showed a significantly increased symptom-free survival ($p < 0.05$). Thus 5 out of 14 rats treated with 11 kBq and 2 out of 5 rats treated with 10 kBq were alive beyond the 67 days follow up period. No signs of bone marrow toxicity or body weight loss were observed in the treated animals. The significant anti-tumour effect of ^{223}Ra at doses that are tolerated by the bone marrow indicate that ^{223}Ra is a promising candidate to eradicate bone metastases. In the same nude rat model breast cancer cells were resistant to high doses of cisplatin, doxorubicin, and an immunotoxin (40,41), as well as to both pamidronate Aredia^{R} and ^{131}I-labeled bisphosphonate treatment.

Lastly, bio-distribution studies in dogs have revealed a similar affinity for and stability within calcified tissues. Autoradiography of canine specimens indicated concentration of radioisotope on the bone surfaces and a very high accumulation in tumours forming bone-matrix (data not shown).

Clinical experiences with Alpharadin®

Thirty-one patients, 10 with breast cancer and 21 with prostate cancer, all with metastases to the skeleton, have so far been enrolled in phase I A and phase I B trials. (42-44) The primary objective was to evaluate the safety and tolerance of the drug. The toxicity was monitored using NCI common toxicity criteria and the quality of life was assessed in all patients according to EORTC QLQ-C 30. Blood clearance of ^{223}Ra was studied in the initial 25 patients.

In the first part of the study, 25 patients were given intravenously a single injection of ^{223}Ra. Groups of 5 patients were treated with increasing dose-levels and were followed weekly for 8 weeks. Dose-levels ranged from about 40 to 200 kBq/kg^{-1} b.w.

In the second part of the study the tolerability of repeated doses was studied. Six patients with metastatic prostate cancer were

treated, two with 100 kBq kg^{-1} b.w. x 2 at six-weeks intervals, and four with 40 kBq kg^{-1} b.w. x 5 at three-weeks intervals.

Dose-limiting toxicity was not observed in the dose escalating part of the study. Reversible myelosuppression occurred, with nadir 2-3 weeks after injection and recovery during the follow-up period. Neutropenia of maximum grade 3 occurred in two out of the 25 patients. The thrombocytes revealed only grade 1 toxicity, even at the two highest dose levels. Few adverse events were seen, nausea being the most frequent one occurring in four out of five patients at the highest dose level. Reversible diarrhoea, grades 1 and 2, responding well to medication, were occasionally observed in all dose groups.

Several patients reported pain palliation. In all patients a decline in S-ALP values was observed. A reduction by more than 50% of the baseline was observed, primarily in patients with elevated pre-treatment values.

In six patients where gamma-camera scintigraphy was performed, accumulation of ^{223}Ra was observed in skeletal lesions similar to that seen in diagnostic bone-scans with ^{99m}Tc-MDP. The blood radioactivity level at 10 min post injection was 12 % of the initial value. It was further reduced to 6 % at 1 hour and to less than 1 % after 24 hours (42).

Future developments

It is a general experience in oncology that the combined use of different treatments will improve the patient outcome.

A strategy for the use of ^{223}Ra followed by bisphosphonate treatment is now being explored. The rational is that the first step may eradicate, or at least reduce the number of clonogenic tumour cells, whereas the subsequent bisphosphonate administration will cover the treated areas and then exert an osteoprotection, analogous to a "teflon coating of surfaces". Preliminary experiments indicated that pamidronate treatment alone did not improve survival, but treatment with bisphosponate shortly after ^{223}Ra injection tended to improve therapeutic responses at higher amounts of radioactivity. Possibly, bisphosphonate prevented osteoclast mediated resorption which could otherwise reduce the dose deposited by the radiopharmaceutical.

We believe that combined treatment; a "sterilise and seal" approach, may, hopefully, accomplish two goals:

1. To reduce the loss of radioactivity from the targeted bony sites.
2. To coat /seal the affected endosteal bony surface, possibly rendering it less accessible and prone to attach new circulating tumour cells.

References

1. Harvie DI. The radium century. Endeavour, 23(3):100-5, 1999

2. Mould, RF. Marie and Pierre Curie and radium: history, mystery, and discovery. Med Phys 26(9):1766-72, 1999

3. Macklis RM. Portrait of Science. Scientist, technologist, proto-feminist, superstar. Science, Mar 1;295(5560)1647-8 2002

4. International Commision on Radiological Protection. Alkaline earth metabolism in adult man. Oxford: Pergamon Press, ICRP Publication 20, 1973

5. Norris WP, Speckman TW, and Gustafson PF. Studies of the metabolism of radium in man. Am J Roentgenology 73, 785-802, 1955

6. Rowland RE. Low level radium retention by the human body: A modification of the ICRP publication 20 retention equation. Health Phys 65(5): 507-513, 1993

7. Aronowitz JN. Dawn of prostate brachytherapy: 1915-1930. Int J Radiat Oncol Biol Phys 54(3):712-718, 2002

8. Mazeron JJ, and Gerbaulet A.The centenary of discovery of radium. Radiother Oncol 49(3):205-16, 1998

9. Early PJ, and Landa ER. Use of therapeutic radionuclides in medicine. Health Phys 69 (5):677-94, 1995

10. Martland, H.S., and Humphries, R.E. Osteogenic sarcoma in dial painters using luminous paint. Arch. Pathol., 7: 406-417, 1929

11. Fry SA. Studies of U.S. radium dial workers: an epidemiological classic. Radiat Res 150(5 Suppl):S21-S29, 1998

12. Wick RW, Nekolla EA, Gøssner W, and Kellerer AM. Late effects in ankylosing spondylitis patients treated with 224Ra. Radiation Res 152, S8-S11, 1999

13. 4Ra treatment in ankylosing spondylitis. J. Nucl Med. 42S: 128P, 2001

14. Nekolla, E.A., Kreisheimer, M., Kellerer, A.M., Kuse, I.M., Gossner, W., and Spiess, H. Induction of malignant bone tumors in radium-224 patients: Risk estimates based on the improved dosimetry. Radiat.Res., 153:93-103, 2000

15. Henriksen G., Alstad, J., Hoff, P. and Larsen, R.H. 223Ra for endotherapeutic applications prepared from an immobilized 227Ac/227Th source. Radiochim Acta, 89: 661-666, 2001

16. Imam SK.Status of radioimmunotherapy in the new millennium. Cancer Biother Radiopharm 16 (3):237-56, 2001

17. Silberstein EB and Williams C: Strontium-89 therapy for the pain of osseous metastases. J.Nucl.Med., 26:345-348, 1985

18. Robinson RG, Blake GM, Preston DF, McEwan AJ, Spicer JA, Martin NL, Wegst AV, and Ackery DM: Strontium-89: treatment results and kinetics in patients with painful metastatic prostate and breast cancer in bone. Radiographics., 9:271-281, 1989

19. Serafini AN: Current status of systemic intravenous radiopharmaceuticals for the treatment of painful metastatic bone disease. Int.J.Radiat.Oncol.Biol.Phys., 30:1187-1194, 1994

20. Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, Porter AT, and Zivanovic MA: A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. Eur.J.Cancer, 1991

21. Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, Sathyanarayana JR, Yakemchuk VN, Thomas GM, Erlich LE, and et, a.: Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. Int.J.Radiat.Oncol.Biol.Phys. , 25:805-813, 1993

22. Robinson RG, Preston DF, Schiefelbein M, and Baxter KG: Strontium 89 therapy for the palliation of pain due to osseous metastases. JAMA, 274:420-424, 1995

23. Silberstein EB: Dosage and response in radiopharmaceutical therapy of painful osseous metastases. J. Nucl. Med. 37: 249-252, 1996

24. Blake GM, Gray JM, Zivanovic MA, McEwan AJ, Fleming JS, and Ackery DM. Strontium-89 radionuclide therapy: a dosimetric study using impulse response function analysis. Br.J.Radiol., 60:685-692, 1987

25. Breen SL, Powe JE, and Porter AT: Dose estimation in strontium-89 radiotherapy of metastatic prostatic carcinoma. J.Nucl.Med., 33:1316-1323, 1992

26. Goeckeler WF, Edwards B, Volkert WA, Holmes RA, Simon J, and Wilson D: Skeletal localization of samarium-153 chelates: potential therapeutic bone agents. J.Nucl.Med., 28:495-504, 1987

27. Resche I, Chatal JF, Pecking A, EllP, Duchesne G, Rubens R, Fogelman I, Houston S, Fauser A, Fischer M, and Wilkins D: A dose-controlled study of 153Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur.J.Cancer, 33:1583-1591, 1997

28. Serafini AN, Houston SJ, Resche I, Quick DP, Grund FM, Ell PJ, Bertrand A, Ahmann FR, Orihuela E, Reid RH, Lerski RA, Collier BD, McKillop JH, Purnell GL, Pecking AP, Thomas FD, and Harrison KA: Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. J.Clin.Oncol., 16:1574-1581, 1998

29. Collins C, Eary JF, Donaldson G, VernonC, Bush NE, Petersdorf S, Livingston RB, Gordon EE, Chapman CR, and Appelbaum FR: Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. J.Nucl.Med., 34:1839-1844, 1993

30. Hall. E.J. Radiology for the Radiologist. 4th ed. Philadelphia, PA: JB Lippincott 1994

31. Paget S. The distribution of secondary growths in cancer of the breast. Lancet, 1: 571-573, 1889

32. Guise TA, Mundy GR. Cancer and bone. Endocr Rev 19(1):18-54, 1998

33. Hassfjell SP, Hoff P, Bruland ØS, and Alstad J: Synthesis and biodistribution of a novel bone seeking alpha-emitting radiopharmaceutical. J.Labelled Compds.Radiopharm., 34:717-734, 1994

34. Larsen, R.H. and Bruland, Ø.S.: Preliminary evaluation of a new radiolabeled bisphosphonate. J. Labelled Compds. Radiopharm., 51, 823-830, 1998

35. Larsen, R.H., Murud, K.M., Akabani, G., Hoff, P., Bruland, Ø.S., and Zalutsky, M.R.: 211At- and 131I-labeled bisphosphonates with high in vivo stability and bone accumulation. J. Nucl. Med. 40, 1197-1203, 1999

36. Hassfjell, S., Ingebrigtsen, K, and Bruland, Ø.S.: Synthesis, purification and biodistribution of 205Bi-DOTMP, visualizing bone deposition patterns with autoradiography. Nucl. Med. Biol., 28, 425-433, 2001

37. Henriksen, G., Fisher, D.R., Roeske, J.C., Bruland, Ø.S., and Larsen, R.H.: Targeting of osseous sites with alpha emitting 223Ra: Comparison with beta emitter 89Sr in mice. J. Nucl. Med., 74/2, 252-259, 2003

38. Kvinnsland, Y., Skretting A., and Bruland, Ø.S.: Radionuclide therapy with bone-seeking radiopharmaceuticals: Monte Carlo calculations of dose-volume histograms for bone marrow in trabecular bone. Physics in Med. & Biol. 46, 1149-1161, 2001

39. Henriksen, G., Breistøl, K, Bruland, Ø.S., Fodstad, Ø., and Larsen, R.: Significant antitumor effect from bone-seeking, alpha particle-emitting radium-223 demonstrated in an experimental skeletal metastases model. Cancer Res., 62, 3120-3125, 2002

40. Engebråten O. and Fodstad, Ø. Site-specific experimental metastasis patterns of two human breast cancer cell lines in nude rats. Int. J. Cancer, 82: 219-225, 1999

41. Engebråten O., Sivam, G., Juell, S and Fodstad, Ø. Systemic immunotoxin treatment inhibits formation of human breast cancer metastases and tumor growth in nude rats. Int. J. Cancer, 88: 970-976, 2000

42. Larsen, R.H., Borch, K.W., Aas, M., Fossaa, S.D., Baltesgard, L., Traasdahl, E., Hess, S., Salberg, G., Henriksen, G., Schoultz, B.W., Nilsson, S., and Bruland, Ø.S.: Phase I clinical trial exploring the alphaemitting radium-223 against skeletal metastases: Blood clearance in patients with breast and prostate cancer. Int. J. Cancer, 13s, 285, 2002

43. Nilsson, S., Balteskard, L., Fossa, S.D., Westlin, J.E.., Borch, K.W., Traasdahl, E., Salberg, G., Larsen, R.H., and Bruland, Ø.S.: Phase I clinical trial exploring the bone-seeking alpha emitter radium-223 in patients with skeletal metastases from breast and prostate cancer. J.Clin. Oncol. Submitted, 2002

44. Nilsson S, Balteskard L, Fossa SD, Westlin JE, Borch KW, Larsen RH, and Bruland OS. Tolerability of a novel bone-seeking radionuclide - the alpha emitter radium-223 - in patients with skeletal metastases from breast and prostate cancer. Abstract for ECCO 12, Copenhagen 21-25 Sep 2003

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