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(54) Title: TREATING DISEASE USING RADIUM-225

(57) Abstract: A method of treating disease, e.g., bone cancer, by the administration of a composition comprising radium-225, for example, radium chloride. The radium-225 can be used in the form of a cationic species, in association with a chelator, or in association with another type of carrier (for example, a molecule, an antibody, a peptide, a protein analog, a chelator-antibody combination, a peptide-antibody combination, an associated fullerene compound, or a lipid).

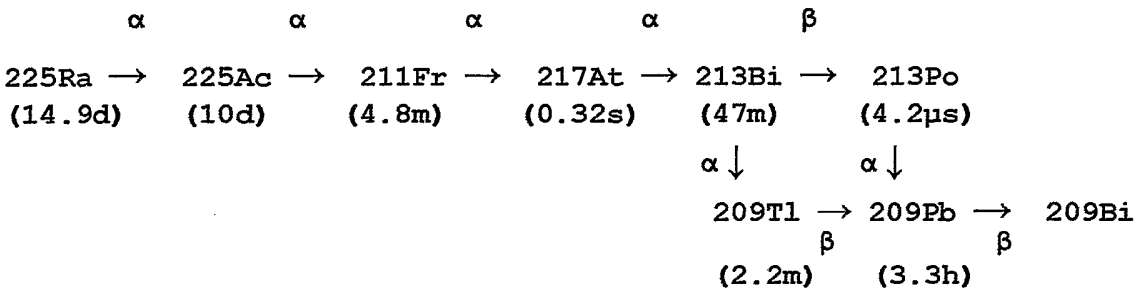
TREATING DISEASE USING RADIUM-225

The present invention relates to the novel use of radium-225 for treatment of disease, e.g., in the treatment of humans.

PCT Published Patent Application No. WO 00/40275 to Anticancer Therapeutic Inventions AS, which relates specifically to the use of radium-223 as a cancer therapeutic, mentions the earlier study and use of two other radium isotopes (radium-224 and 226) for the treatment of cancers, mainly cancer of the bone. No mention of radium-225 is made.

The present invention relies upon the use of radium-225 for analogous purposes to those proposed in the previously mentioned PCT patent document since the 225 isotope does not produce radon in its decay chain and moreover has low energy gamma radiation in its decay chain which is deemed to be an advantage in regard to suppressing "collateral" damage to potentially neighboring non-cancerous cells.

Compared to other radium isotopes, which produce radon (namely, radium-223, radium-224, and radium-226), or high-energy gamma radiation (radium-226 and radium-224) in their decay scheme, radium-225 is a superior radioisotope for cancer treatment. Radium-225 does not have the associated radon or high-energy gamma radiation in its decay chain. This makes handling of this radioisotope safer, as well as reducing the side effects caused by destroying surrounding healthy tissue. The decay of radium-225 is shown below and provides for five alpha decays:



As compared to other radium isotopes, which produce radon (radium-223, radium-224, and radium-226) or which produce high energy gamma radiation (radium-226 and radium-224) in their decay scheme, radium-225 is a superior radioisotope for use in cancer treatment. This makes the handling of this radioisotope safer and also reduces the side effects caused by any destruction of healthy cells.

In addition, recent research with Ac-225 has shown this isotope to be the most cytotoxic agent to date in the treatment of cancer. Concurrently, the follow-up use of radium-225 can add an additional increase in the overall potential cytotoxicity for the treatment and thereby reduce the dose of radioisotope given to the patient.

The present invention relates to a novel use of radium-225 as a beta emitting radiopharmaceutical for palliative treatment with the additive benefit of therapeutic application from the alpha emitting decay products. Radium-225, similar to other radium isotopes, can be used for the targeting of calcified tissues, e.g., bone surfaces and osseous lesions. As an example, the invention may be used for prophylactic cancer treatment by delivering a focused dose to bone surfaces in patients with a high probability of having undetected micrometastases at the bone surfaces. Another example of its potential use would be in the treatment of painful osseous sites

in a similar fashion as the current treatments with beta and electron emitting radiopharmaceuticals for bone pain palliation.

This invention includes the use of the nuclide as a cationic species and/or associated to a chelator or another form of a carrier molecule with affinity for calcified tissues. This also includes, but is not limited to, the combination of radium-223 with a chelator that can be subsequently conjugated to a molecule having affinity for calcified tissue. The intent of this invention is to use the radioisotope to generate a combination of beta and alpha particles on bone surfaces and/or in calcified tumors for the palliation of pain caused by the various diseases and/or the prophylactic use against possible minimal disease to the skeleton and/or also for the therapeutic treatment of established cancer to bone. The diseases where radioisotopes could be used include, but are not limited to, skeletal metastases of prostate-, breast-, kidney-, and lung cancers, as well as primary bone cancer and multiple myeloma.

Radium-225 solutions can be prepared for use in the targeting of calcified tissues or for bone surface irradiation. The proposed therapeutic agent provides the combination benefits of beta radiation (beta energy = 358.7 keV) from the radium-225 decay and the alpha radiation from the decay products. The low energy beta dose will minimize the associated crossfire effect to the supporting bone marrow and will reduce potential toxicity effects. The half-life of radium-225 ($t_{1/2}$ = 14.9 days) will allow for adequate time for the radium-225 to be adsorded by the cancerous site(s). This will minimize the translocation of the decay products. The virtual nonexistence of radon in the radium-225 decay chain ensures less translocation of daughter nuclides than from the radium-226, radium-224, and radium-223 series.

Any method known to the person in the art in regard to the production and/or isolation of radium-225 can be utilized in

practicing the present invention. For example, U.S. Patent No. 5,355,394 (assigned to EURATOM) describes the irradiation of radium-226 in a thermal neutron flux of a nuclear reactor to obtain an irradiation product containing thorium-229, chemically isolating a thorium fraction from that product, chemically separating from that fraction actinium-225 and radium-225, with the subsequent separation of radium-225 by known means.

Another way to produce radium-225 which has been recently been disclosed in described in U.S. Patent No. 6,208,704 to L.M. Lidsky (assigned to MIT) wherein radium-226 is irradiated to a high energy photon beam to isotopically convert the starting isotope.

All available administration routes, such as oral, subcutaneous, intravenous, intraarterial, or transcutane can be used to administer the radium-225 salt or derivative. Preferably, the active compound is by administered by injection or infusion.

The active principle according to the invention could be used both in prophylactic, palliative and therapeutic treatment of non-malignant and malignant diseases affecting bones and soft tissues. The malignant diseases can be selected from the following: prostate cancer; breast cancer; kidney and urinary cancer; primary bone cancer; lung cancer; and multiple myoloma. The non-malignant diseases can be selected from the following: autoimmune disease affecting joint and skeleton, e.g., rheumatoid arthritis; schleroderma; and spondyloartropathies.

The radium-225 can be used in the form of a cationic species (e.g., radium-225 chloride), in association with a chelator, or in association with another type of carrier (for example, a molecule, an antibody, a peptide, a protein analog, a chelator-antibody combination, a peptide-antibody combination, an associated fullerene compound, or a lipid). For example, the physiologically acceptable preparation for in-vivo

administration according to the present invention comprises dissolving radium-225 salt, with or without a single or a combination of several cations, as stabilizing alkaline earth metal cation analogue carrier, with or without an agent to prevent precipitation and/or generation of colloids, in addition to pharmacologically acceptable carriers and adjuvants.

The concentrations of the compounds in the preparation will generally be less than the individual LD_{50} dose, for example, less than 20% of the individual LD_{50} dose, and thus will vary for the different embodiments in which this therapeutic can be administered. The activity of the radium-225 will be dependent upon the type and route of administration and the underlying condition or disease and will generally vary from about 50 kBq to about 10 MBq, administered in either single or multiple doses.

The radium-225 therapeutic of the present invention can be used in combination therapy where the radium-225 preparation is combined with the following classes of treatment: chemotherapy (including bisphosphonates); surgery; external beam irradiation; low LET radiation; bone emmiting - bone seeking radiopharmaceuticals; gene therapy; and/or hormonal treatment.

A test of the present invention in mice via a Ra-225 distribution study for use in bone palliation from bone palliation was conducted. Two microcuries of substantially pure Ra-225, freshly prepared so as to be substantially free of daughter Ac-225) was injected as a citrate solution into six BALB/c mice. The mice were sacrificed at one hour, twenty-four hours, and six days post-injection. Ten organs were analyzed for both Ra-225 and daughter Ac-225 concentrations at the time of sacrifice. Significant localization of the Ra-225 was seen in the long bones with low uptake in the other organs. The daughter actinium was also confined to the targeted areas and

was thus well tolerated. The maximum tolerated dose reached 0.7 microcuries per mouse.

The foregoing mouse study is presented for illustrative purposes only and should not be construed in a limiting sense. The scope of protection desired is set forth in the Claims that follow.

I Claim:

1. A method of treating disease by the administration of a composition comprising radium-225.

2. A method as claimed in Claim 1 wherein the composition comprises radium-225 chloride or other radium-225 salt compound.

3. A method as claimed in either Claim 1 or 2 wherein the administration is by injection.

4. A method as claimed in either Claim 1 or 2 wherein the administration is by infusion.

5. A method as claimed in either Claim 1 or 2 wherein the radium-225 is associated with a carrier.

6. A method as claimed in Claim 5 wherein the carrier is an antibody.

7. A method as claimed in Claim 5 wherein the carrier is a chelator-antibody combination.

8. A method as claimed in Claim 5 wherein the carrier is a peptide.

9. A method as claimed in Claim 5 wherein the carrier is a protein analog.

10. A method as claimed in Claim 5 wherein the carrier is a chelator-antibody combination.

11. A method as claimed in Claim 5 wherein the carrier is a peptide-antibody combination.

12. A method as claimed in Claim 5 wherein the carrier is a fullerene compound.

13. A method as claimed in Claim 5 wherein the carrier is a lipid.