Review Article

Actinium-225 in Targeted Alpha Therapy

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Abstract

The utilization of actinium-225 (^{225}Ac) radionuclides in targeted alpha therapy for cancer was initially outlined in 1993. Over the past two decades, substantial research has been conducted, encompassing the establishment of ^{225}Ac production methods, various preclinical investigations, and several clinical studies. Currently, there is a growing number of compounds labeled with ^{225}Ac that are being developed and tested in clinical trials. In response to the increasing demand for this nuclide, production facilities are either being built or have already been established. This article offers a concise summary of the present state of clinical advancements in compounds labeled with ^{225}Ac. It outlines various processes involved in the production and purification of ^{225}Ac to cater to the growing demand for this radionuclide. The article examines the merits and drawbacks of different procedures, delves into preclinical trials, and discusses ongoing clinical trials.

Keywords: Actinium-225, alpha emitter, nuclear medicine, oncology, targeted alpha therapy

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Introduction

The reckless enhancement and expansion of unusual cells in different organs of the body are known as cancer. Together with large and latest technological advancements in oncology, treatments of advanced cancer are still a challenging phenomenon. Oncological treatments can be classified as surgery, radiotherapy, and chemotherapy. In addition, there are several types of therapies like hormone therapy, gene expression modulators, inducers of apoptosis, and signal transduction inhibitors, and more are available clinically or under observation. Various deadly cancers might be controlled and toxicity in normal tissue could be reduced by new emerging targeted therapies. In radiation oncology, targeted alpha therapy (TAT) is such kind of systemic therapy that can control the disease. In the field of radiation oncology, TAT stands out as a systemic treatment capable of disease control. Isotopes such as actinium-225 (^{225}Ac), ^{212}Bi, ^{212}Pb, ^{223}Ra, ^{149}Tb, ^{227}Th, and ^{211}At have demonstrated promise in both preclinical investigations and clinical trials.[1] The nature of these particles is also important because of their biological effect. The primary characteristics of an α particle are its linear energy transfer (LET) and its distance traveled (path length).[2]

α particles of higher LET (100 KeV/μm), increased energy (2–10 MeV), and path length (50–100 μm) have relatively higher DNA double-strand breaking probability than β emitters although it generates high toxicity. The short path length of α-emitters lessens irradiation in surrounding healthy cells. Therefore, the potential for unintended radiation exposure to undamaged bodily tissues and organs may be minimized. ^{225}Ac emerges as a compelling choice TAT due to its capacity to generate multiple daughter isotopes through a sequence of four α particles and two β particles decays within a relatively brief timeframe. This attribute enhances the therapeutic impact of substances labeled with ^{225}Ac.[3] The cancer therapy community and pharmaceutical industries have taken under consideration the potentiality of α particles for conjugated antibodies, drugs, and antibody conjugation. The direction of pathways has also created the ambiance through so many clinical and preclinical studies.[4] However, the hindrance in the progress of TAT has consistently been the limitations associated with half-lives and availability. For a few years, increasing knowledge in the production process and radiochemistry has made α-emitters more demandable in cancer treatment.

Radionuclides used in TAT need to be conjugated to target vectors such as nanocarriers, peptides, biomolecules,

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monoclonal antibodies (MABs), and small-molecule inhibitors. The success of targeted radiotherapy relies on the trajectory of its radionuclide, the behavior of particles, and their biological effects which need to align with given tumor mass, size, heterogeneity, and radio sensitivity.[5]

^{225}Ac emerges as a highly promising choice for TAT owing to its favorable characteristics. These include a prolonged half-life of 10 days, which aligns effectively with targeting vectors based on antibodies. In addition, its four high-energy alpha emissions make it exceptionally effective in causing cell lethality.[6-8] In both laboratory-based and living organism-based models, ^{225}Ac demonstrates notably higher potency compared to its daughter nuclide, ^{213}Bi.[9] The augmented effectiveness of ^{225}Ac in comparison to ^{213}Bi ($T_{1/2}$ ~ 46 min) can be ascribed to its significantly longer half-life, which is 313 times greater, along with the emission of three additional alpha particles.[10] In this review, we aim to provide a comprehensive overview of the current progress in clinical research involving ^{225}Ac-labeled compounds. We discuss the synthesis and purification processes of ^{225}Ac to meet the increasing demand for this radioactive element, evaluate the efficacy and limitations of different production methods, and review both preclinical and clinical trials conducted. Through this analysis, we aim to offer insights into the advancements, challenges, and potential applications of ^{225}Ac in TAT.

Actinium-225

^{225}Ac has 32 isotopes and is the first substance of the actinide series. ^{228}Ac and ^{227}Ac are naturally formed through the decay sequences of ^{232}Th and ^{235}U, respectively. ^{225}Ac from the ^{237}Np decay chain which disappeared in nature and then manufactured again and its disintegration takes six steps to reach stable nuclei which have a half-life of 10 days. The production of ^{225}Ac and its daughter ^{213}Bi is derived from ^{233}U, engendered during a scientific endeavor encompassing the neutron bombardment of ^{232}Th in the 1960s.[11] ^{233}U has been directed to ^{229}Th ($T_{1/2}$ ~ 7340 year). A portion of ^{229}Ac is also collected from the decay of ^{233}Th recently.[12] Figure 1 shows the decay scheme of 225Ac.

The key challenge for using ^{225}Ac in TAT that is preventing to reach its complete clinical efficacy is the inadequacy of the quantities of ^{225}Ac producible by prevailing methodologies, limiting its viability for widespread clinical applications. The total estimated production of ^{225}Ac is 63 GBq/year, which is not adequate for the clinical and preclinical experiments.[13] An amount of 26.64 GBq is available at the Institute of Physics and Power Engineering (IPPE) in Obninsk, Russia. Furthermore, the same quantity of pure ^{225}Ac has been supplied per year by ORNL (Oak Ridge National Laboratory) since 1997. The Institute for Transuranium Elements in Karlsruhe, Germany (ITU) oversees a diminutive ^{229}Th source endowed with the capacity to generate a maximum of 12.95 GBq of ^{225}Ac.[14] Various research laboratories are currently exploring alternative production methods utilizing high-energy accelerators. It is anticipated that the ongoing investigations will lead to solutions for the production challenges in the coming years.[15-19] In the clinical field, recent demand for ^{225}Ac is almost 185 GBq per year based on the use of ^{225}Ac for therapy, and the future estimated demand is about 200–400 GBq per year.[20] Consequently, few processes have been developed to meet the demand of ^{225}Ac. Figure-2 gives a comparison of various production methods of 225Ac in terms of production yield per year.

Generation Procedures

^{225}Ac production by Th-GEx method

The generator method, considered the most convenient and promising approach, is used to produce ^{225}Ac by isolating it from the parent radionuclide ^{229}Th. This parent radionuclide is created through the decay process of ^{233}U. This ^{233}U is produced in nuclear reactors through a specific reaction where ^{232}Th absorbs a neutron (^{232}Th [n, γ]) and transforms into ^{232}Th, which then decays with a half-life of 23.5 min to form ^{233}Pa (^{233}Th [β, 23.5 min] → ^{233}Pa). This ^{233}Pa undergoes subsequent decay with a radioactive half-life of 27.4 days, ultimately culminating in the formation of ^{233}U (^{233}Pa [β, 27.4 days] →^{233}U).[21] Globally, almost higher than 95% of ^{225}Ac is produced by the generator extraction method from ^{229}Th (Th-GEx method). The process involves dissolving ^{229}Th in 8M nitric acid, followed by the use of anion exchange resins to separate the mixture of ^{225}Ac and ^{225}Ra. Subsequently, individualized ^{225}Ac is acquired through supplementary refinement processes, encompassing potential techniques such as cationic exchange columnar,[22] solid-phase extraction chromatography,[23] or a synergistic application of anionic and cationic exchange resin systems,[22] discrete ^{225}Ac can be obtained. This results in the extraction of immaculate ^{225}Ac around 80%–95% for preclinical and clinical applications. The ^{299}Th generator is capable of producing an annual yield reaching 33.3 GBq,[5] which is equivalent to a daily output of approximately 90.41 MBq. In addition, the production capacity of A research institute is projected to be around 1.85 GBq[24] of ^{225}Ac on a monthly basis, which roughly equates to a daily production of about 61.6 MBq.

Production of actinium-225 through thorium proton spallation

The augmentative potential of ^{225}Ac production can be realized through the employment of cyclotrons for the irradiation of natural ^{232}Th targets with protons exhibiting medium to high energy.[25] The direct production of ^{225}Ac from ^{232}Th targets can be achieved by utilizing high-energy protons ranging from 78 to 192 MeV. This technique has the potential to generate curie quantities of ^{225}Ac.[14] A quantity of 1.54 curies of ^{225}Ac can be synthesized during a 10-day irradiation period involving a 5 gcm^{-2} thorium target at BNL-BLIP, utilizing meticulously adjusted beam currents of 100 μA and incident proton energies at 192 MeV. This resultant production equates to an approximate daily output of 4748.3 MBq, with a corresponding ^{227}Ac/^{225}Ac

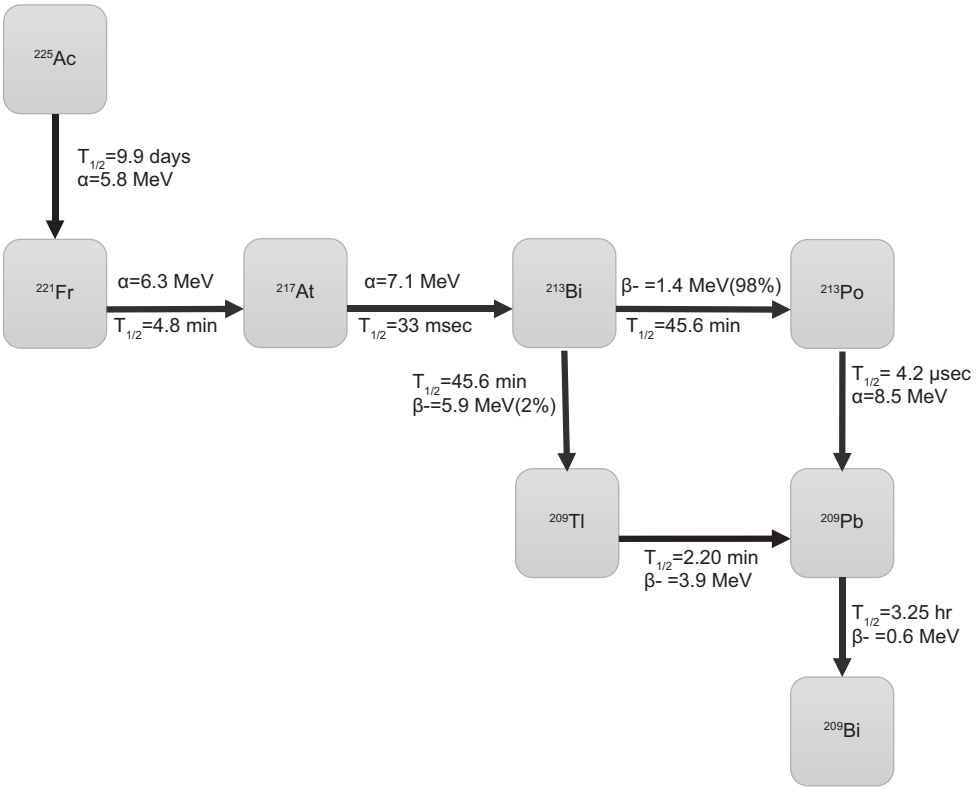

Figure 1: Decay scheme of actinium-225

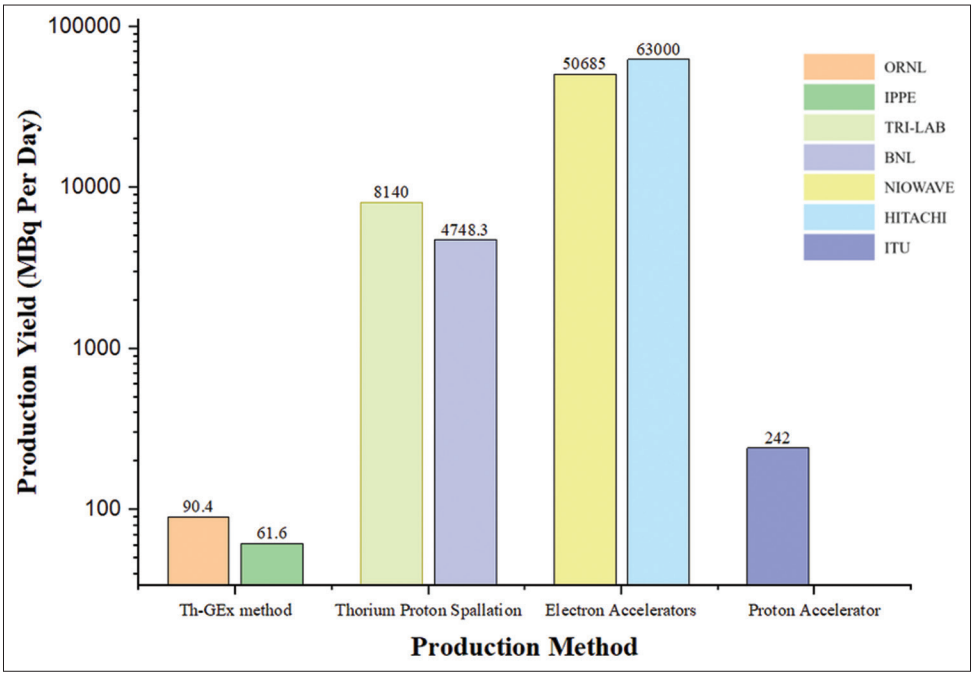

Figure 2: Daily production of actinium-225 through different production methods across various laboratories

ratio of 0.20%.[26] The Tri-Lab project team is exploring methodologies for the direct extraction of ^{225}Ac from thorium targets that have been irradiated with protons. In an experiment that spanned 10 days, a proton beam with an energy of 200 MeV was irradiated at 165 μA, successfully yielding 81.4 GBq of ^{225}Ac[27] roughly translating to an approximate daily output of 8140 MBq. A method for producing a ^{225}Ac generator from thorium irradiated with protons has been developed at TRIUMF, which minimizes the undesirable ^{227}Ac byproduct to a level of 0.1 − 0.3% relative to the ^{225}Ac activity.[28] Another

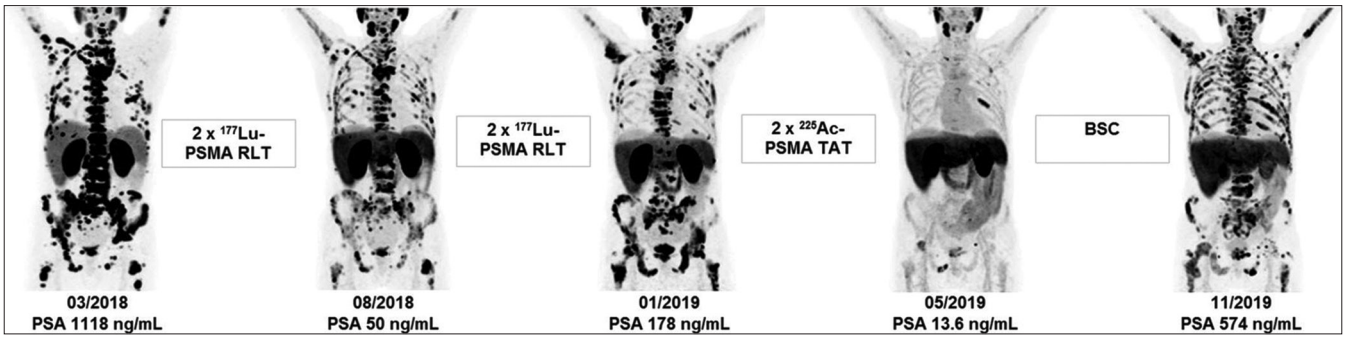

Figure 3: A 79-year-old metastatic castration-resistant prostate cancer patient (patient 11) with lymphatic and bone metastases. The patient received two cycles of 177Lu-PSMA RLT (cumulative activity, 10.5 GBq) after the failure of docetaxel and showed an initial response. However, disease progression was observed in January 2019 after two additional 177Lu-PSMA RLT cycles (cumulative activity, 12 GBq), and the patient was admitted for actinium-225-PSMA-I and T TAT. PSA follow-up and PSMA PET showed impressive response after two cycles (cumulative activity, 13.4 MBq). Unfortunately, the patient developed grade 3 leukocytopenia, and TAT could not be continued. Disease progression was observed in November 2019 after best supportive care (BSC)[49]

significant hurdle in this process is the isolation and refinement of ^{225}Ac from the radionuclides that are coproduced.[29] A unique precipitation-based thorium debulking method is introduced for the chemical separation process to isolate ^{225}Ac from most other elements and yield ^{225}Ac with minimal ^{227}Ac content. This procedure entails the precipitation of thorium peroxide, employing cation exchange to diminish the dimensions of chromatographic columns, processing durations, and the magnitude of liquid radioactive waste, along with the utilization of extraction chromatography for the isolation of ^{225}Ac from other elemental constituents. Compared to other thorium precipitates, such as thorium oxalate or thorium iodate, this method offers better filtration performance and less interference.[13]

Actinium-225 production by electron accelerators

In an alternative method for generating ^{225}Ac, a tungsten target is subjected to an incident electron beam, resulting in the production of bremsstrahlung photons. Employing a 20 mg ^{226}Ra initiator positioned at a distance of 12.5 cm from the tungsten substrate, this procedure yields 2.44 MBq of ^{225}Ac. Using this method, it is feasible to obtain a monthly yield of 48 GBq of ^{225}Ac from a 1g ^{226}Ra initiator.[30] This method necessitates a potent linear accelerator (LINAC) featuring an extended pulse duration, optimal current intensity, and practical high-frequency generation for efficient production. In addition, implementing this technique can contribute to the diminution of ^{226}Ra nuclear waste.[31] Niowave's superconducting linear accelerators demonstrate the capability to handle a significant annual production exceeding 500 curies of ^{225}Ac, employing a 20 MeV, 210 kW beam, equivalent to approximately 50,684.9 MBq per day.[32] Hitachi reported that this effective technique yielded a substantial quantity of 63000 MBq of ^{225}Ac, derived from a ^{226}Ra target, utilizing electron linear accelerators operating at energy levels ranging from 27-44 MeV and irradiated by electron currents ranging from 61 to 160 μA for 24 h.[33] An alternative method for producing ^{225}Ac involves utilizing a photonuclear reaction ^{226}Ra(γ, n) ^{225}Ra (β, 14.8 days) → ^{225}Ac using either a microtron[34] or a linear electron accelerator.[30,31] When subjecting ^{226}Ra to radiation, it undergoes a transformation into ^{225}Ra by (γ, n) reaction, which requires a certain period of time after irradiation to naturally decay into ^{225}Ac. This duration is known as the cooling time and is necessary for ^{225}Ra to reach its peak activity before it can be utilized effectively.[35] One notable drawback of the procedure for producing ^{225}Ac through photonuclear reactions is the utilization of highly radioactive and emanating targets, as well as the need for powerful electron accelerators. However, a significant advantage of its photonuclear production is the potential to make use of old radioactive waste that contains Ra. This means that existing radioactive waste, which may have limited practical applications, can be repurposed to produce valuable ^{225}Ac through the photonuclear method.[36]

Actinium-225 production by proton accelerators

Several approaches have been developed to produce ^{225}Ac using accelerators. Among these methods, the most favorable one for generating ^{225}Ac on a large scale is the utilization of a cyclotron to irradiate a ^{226}Ra target with protons, leading to the transformation of ^{226}Ra into ^{225}Ac through the process of ^{226}Ra (p, 2n) ^{225}Ac.[26] This method is used to generate ^{225}Ac by providing photon energy of 16.8 MeV in a medical cyclotron, which is demonstrated experimentally for the first time.[15] The benefit of utilizing this reaction is that it does not coproduce any other long-lived actinium radioisotope, such as ^{227}Ac, thereby ensuring the purity of the ^{225}Ac produced.[19] This method is considered the most viable approach due to the utilization of low proton energy. The Institute for Transuranium Elements (ITU) managed to produce approximately 485 MBq of ^{225}Ac by subjecting a $RaCl_2$ target to a 28 MeV beam for 45.3 h at a beam current of 50 μA, resulting in an estimated daily output of 4748.3 MBq of ^{225}Ac.[27] Many cyclotrons are already being used worldwide where more than 550 cyclotrons have energy over 16MeV. Due to fulfilling the clinical needs of ^{225}Ac in treatment, proton accelerators can provide a large number of productions of ^{225}Ac. Theoretically, a single-energy beam of 20 MeV on 1g ^{226}Ra can generate 4 TBq of ^{225}Ac per month.[37]

Actinium-225 production in nuclear reactors and challenges of ^{226}Ra irradiation

Nuclear reactors are the most popular source for medical isotopes. However, the production of ^{225}Ac through reactors is still limited. ^{225}Ra can be generated by ^{226}Ra (n, 2n) ^{225}Ra reaction and intense root of high (>6.4 MeV) neutrons that will be controlled by an extremely toxic actinium ^{227}Ac ($t_{1/2}$ ~ 21.8 y) isotope. This method is still not observed experimentally.[13] Although a sufficient amount of ^{225}Ac could be possible to generate. Still, there are some challenges like safely handling the vast resource of ^{226}Ra and production cost. In the 1920s, the extensive production of ^{226}Ra, the only stable isotope closely related to ^{225}Ac with a prolonged half-life, made it the primary radioactive material for meeting both medical and commercial needs. This is due to its suitability as a target material for the production of ^{225}Ac, driven by the demand in the medical and commercial sectors. However, due to the severe radiotoxicity of the substance, its reactivity with liquids and gases, and its degradation into ^{222}Rn gas, the production of the substance was discontinued in 1960.[38] The new source of extracting ^{226} Ra from uranium ore contains 257 mg of ^{226} Ra for each ton of U_3O_8,[39] which is almost 12.85 kg of ^{226}Ra per year. However, the required infrastructure for this production is difficult and expensive.

Radiochemistry

A radiopharmaceutical contains radioisotope discharge alpha, beta, or gamma particles for therapeutic or diagnostic purposes. It is mandatory to study the physical and chemical properties of a radioisotope before clinical and preclinical assay. Most of the radiopharmaceuticals in nuclear medicine are now based on radiometal that has four parts: a linker, a targeted biomolecule (proteins and lipids), a bifunctional chelating agent (ethylenediaminetetraacetic acid [EDTA] and n-hydroxyethyl ethylenediaminetriacetic acid), and the radionuclide (^{225}Ac, ^{213}Bi, ^{111}In, and ^{117}Lu).[40] All actinium found in an aqueous solution with oxidation number (III) are not stable and very much limited which demands a stable chelating agent between the radionuclide and carrier molecule. Furthermore, intravenously injected ^{225}Ac's high toxicity can be lessened by chelating. Mostly used bifunctional chelators are DTPA (Diethylenetriaminepentaacetic acid, N3O5), DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, N4O4), EDTA, PEPA (1,4,7,10,13 pentaazacyclopentadecane-N, N', N", N"', N""-pentaacetic acid, N5O5), CHX-A"-DTPA (cyclohexyl-diethylenetriaminepen- taacetic acid, N3O5), and HEHA, where few of them are in clinical trials. Among them, HEHA is the most favorable, which is a macrocycle compound with a maximum coordination number of 12, comprising 6 nitrogens and 6 carboxylates. Radiometals possessing an ionic radius exceeding 0.9 Å showed constant stability to HEHA, while the Ac^3 + ionic radius is 1.12 Å which showed a fruitful result.[13] Another macrocyclic amide DOTA that has an intense affinity to trivalent ions is conjugated with ^{225}Ac through the carboxyl group. ^{225}Ac-DOTA expresses steadiness in preclinical studies which further led to study about effective DOTA derivatives like MeO-DOTA-NCS, creating the path to link with biomolecules through amino acid residues of antibodies.[41]

Table 1: Recent clinical state of ^{225}Ac

Cancer type	Radio conjugate	Patients	Reference/ government identifier
Leukemia	^{225}Ac-anti-CD33-mAb	76	[44]
Glioma	^{225}Ac-substance P	20	[44]
Neuroendocrine tumors	^{225}Ac-DOTATOC	39	[44]
Prostate cancer	^{225}Ac-PSMA617	400	[44]
mCRPC	^{225}Ac PSMA	20	NCT04225910
AMI	^{225}Ac-HuM195	72	NCT02575963

AML: Acute myeloid leukemia, mCRPC: Metastatic castration-resistant prostate cancer

Clinical Perusal

The recent clinical state of ^{225}Ac is given in Table 1. A clinical trial of a new treatment for neuroendocrine tumors using a small molecule with ^{225}Ac attached to it, called ^{225}Ac-DOTATOC, began in 2011 by a joint team from JRC Karlsruhe and University Hospital Heidelberg.[40] The investigation determined that the maximum dose that could be tolerated in a single administration was 40 MBq. Treatment was started with 39 patients where an initial dose of 18.5 MBq and a cumulative dose of 75 MBq were provided in a 2-month interval. Patients' responses were obtained.

For prostate cancer, treatment development of ^{225}Ac-PSMA617 is considered a milestone in TAT. A clinical test of ^{225}Ac-PSMA617 was started primarily by JRC Karlsruhe and University Hospital Heidelberg and they extended to Steve Biko Academic Hospital, Pretoria, and Technical University, Munich, in 2013/2014. The presence of a substantial amount of PSMA617 enables the capture of decay daughters from ^{225}Ac, leading to targeted cell death while mitigating the toxic effects of the daughter nuclides. ^{225}Ac-PSMA617 was used in the clinical trial under some protocol based on dosimetry estimate, effective tolerability of salvage. A group of 14 patients diagnosed with advanced-stage prostate cancer underwent a treatment regimen involving the administration of 100 kBq/kg of ^{225}Ac-PSMA617 per treatment cycle, which was repeated twice with an interval of 8 weeks between cycles. Due to xerostomia (dry mouth syndrome), 10% of patients' treatments have to be discontinued. During the initial cycle of the subsequent investigation, a standardized dose of 8 MBq, equivalent to 100 kBq/kg based on the body weight of an average patient weighing 80 kg, was administered for further evaluation.[42] To minimize damage to the salivary glands, the subsequent cycles of administration were adjusted based on patient response, with reduced doses ranging from 7 to 4 MBq. The dosage de-escalation was implemented to mitigate potential harm while considering individual patient reactions.[43] Figure 3 shows such a case where ^{225}Ac PSMA-

Table 2: Ongoing trials

Drugs	Disease	Phase	Start date	End date	Participants	Study sponsor	Government identifier
JNJ-69086420	Adenocarcinoma and prostatic neoplasms	1	November 12, 2020	Estimated primary completion: 2025-03-19 Estimated final completion: 2025-07-16	76	Janssen Research and Development, LLC	NCT04644770
^{225}Ac-J591	Prostate cancer	1	October 10, 2017	Primary - January 7, 2021 Final - July 2024	32	Weill Medical College of Cornell University	NCT03276572
^{225}Ac-PSMA617 68Ga-PSMA-11	Prostatic neoplasms, castration-resistant	1	April 1, 2021	November 12, 2025	60	Novartis Pharmaceuticals	NCT04597411
^{225}Ac-J591 Pembrolizumab	Prostate cancer	1 and 2	August 12, 2021	Primary completion: June 2025 Final completion: June 2028	76	Weill Medical College of Cornell University	NCT04946370
[^{111}In]-FPI-1547 [^{225}Ac]-FPI-1434 (multidose) Biological: FPI-1175 Infusion	Advance solid tumors	1 and 2	January 17, 2019	Estimated primary completion: June 2024 Final completion: June 2026	253	Fusion Pharmaceuticals Inc	NCT03746431
^{225}Ac-J591	Prostate cancer	1	August 18, 2020	Estimated primary completion: June 30, 2025 Final completion: June 30, 2027	105	Weill Medical College of Cornell University	NCT04506567
^{225}Ac-J591 with ^{177}Lu-PSMA-I and T ^{68}Ga-PSMA-11	Prostate cancer	1 and 2	June 30, 2021	Primary completion: December 24, 2024 Final completion: December 27, 2027	48	Weill Medical College of Cornell University	NCT04886986
^{225}Ac-FPI-2059, ^{111}In-FPI-2058	NTSR1-expressing solid tumors	1	February 7, 2023	Estimated primary completion: June 2025 Final: September 2025	42	Fusion Pharmaceuticals Inc	NCT05605522
^{225}Ac-FPI-2265 (PSMA-I and T)	mCRPC	2	December 16, 2021	Estimated primary completion: December 16, 2023 Final: December 16, 2024	100	Excel Diagnostics and Nuclear Oncology Centre	NCT05219500
RYZ101, Everolimus 10 mg, Sunitinib 37.5 mg	GEP-NET	3	March 3, 2022	Estimated primary completion: July 2027 Final: July 2028	288	RayzeBio Inc	NCT05477576
RYZ101 with carboplatin, etoposide, and atezolizumab	ES-SCLC	1	October 10, 2022	Estimated primary completion: April 2024 Final: December 2026	31	RayzeBio Inc	NCT05595460
^{225}Ac-lintuzumab + cladribine, cytarabine, filgrastim, and mitoxantrone	Acute myeloid leukemia	1	May 22, 2018	October 2024	26	Medical College of Wisconsin	NCT03441048
^{225}Ac-lintuzumab with venetoclax	Acute myeloid leukemia, relapsed adult AML	1 and 2	January 15, 2020	Primary completion: November 2023 Final: June 2024	38	Actinium Pharmaceuticals	NCT03867682

GEP-NET: Gastropancreatic neuroendocrine tumors, ES-SCLC: Extensive stage small lung cancer, AML: Acute myeloid leukemia, mCRPC: Metastatic castration-resistant prostate cancer, NTSR1: Neurotensin receptor 1

617 appears to be effective against prostate cancer however this trial was stopped due to complexities developed in the patient.

Humanized monoclonal antibody HuM195 (anti-CD33)

The effectiveness of this antibody has been scrutinized in clinical examinations, and deployed concomitantly with chemotherapeutic interventions, directed toward the cellular membrane antigen CD33 correlated with myelomonocytic differentiation. From November 1999 to April 2001, among 191 patients, almost 69 patients were treated with MEC (Mitoxantrone 8 mg/m^2, Etoposide 80 mg/m^2, and Cytarabine 1g/m^2) (P = 0.28). Survivals were 156 days, including a

Table 3: Preclinical trials of ^{225}Ac

Bi-complex	Molecular target	Analysis in	Disease	Dose escalation	Outcome	Reference
[^{225}Ac] Ac-DOTA-TDA-Lipiodol	HCT116	Female and male NCG mice	Hepatic tumors	37 kBq	Significant improvement was observed	[50]
[^{225}Ac] Ac-SibuDAB	PSMA-positive PC-3 PIP and PSMA-negative PC-3 flu	Female FVB mice	Prostate cancer	30 kBq	Increase the risk of radionephrotoxicity	[51]
^{225}Ac-PSMA-617	RM1-PGLS cells	Mice	Prostate cancer	30 kBq	Reduces tumor burden and improves TTP and survival	[52]
	PSMA-positive PC-3 PIP and PSMA-negative PC-3 flu	Female FVB mice	Prostate cancer	30 kBq	Increase the risk of radionephrotoxicity	[53]
	RM1-PSMA+++	NSG mice	Prostate cancer	40 kBq	Enhanced radiation-induced cytotoxicity	[54]
	C4-2, C4-2B, or 22Rv1	NSG mice	Liver, lungs, spleen, stomach, and bone metastases	40 kBq	Antitumor activity	[55]
	C4-2 cell	NSG mice	Prostate cancer	20, 40, and 100 kBq/mouse	Significant tumor growth retardation and improved survival	[56]
^{225}Ac-NZ-16	NCL-H226 cell line	*In vitro*	Mesothelioma	11.1 kBq, 18.5 kBq	Demonstrated a strong antitumor impact with minimal noticeable side effects	[57]
^{225}Ac-DOTA-SCN-antibody, ^{225}Ac-DOTA	C4-2B, LNCaP, and PC3-PIP, PC3	Male NSG mice	Prostate cancer	4.63 kBq	Tumor was removed	[58]
^{225}Ac-crown-αMSH	B16F10	*In vivo* (mice)	Melanoma tumors	4.1±1.9 MBq/nmol	Displays exceptional ratios between target tissue and normal tissue	[59]
^{225}Ac-RPS-074	LNCaP cells	*In vitro*, *in vivo* (male mice)	Prostate cancer	148 kBq	Treatment was more effective and less harmful and almost 86% of tumor was reduced	[59]
^{225}Ac-Au@TADOTAGA	U-87 MG	Female SCID mice	Glioblastoma	1 kBq	Retardation of tumor growth	[60]
[^{225}Ac] [Ac (H4py4pa)]	HER-2 Cell line-SKOV-3	Female NRG mice	Ovarian cancer	10.1±0.7 kBq	Showed good response *in vitro* serum stability and tumor specificity	[61]
[^{225}Ac]-PRIT ^{225}Ac-DOTA-PEG7-Tz	Carbohydrate antigen 19.9 Cell line BxPC3	Athymic nude mice (in biodistribution, *ex vivo, vivo*, dosimetry)	PDAC	18.5 kBq *In vivo* (9.25, 18.5, or 37 kBq)	Showed higher accumulation on different organs. No significant tumor reduction was noticed	[62]
[^{225}Ac] hu11B6	Kallikrein peptidase 2(hK2) Cell line MFM-223 and BT-474	Female athymic BALB/c nude mice	Breast cancer	A single dose of 11.1 kBq on 5 μg antibody)	No significant accumulation in any organ. Increased survival	[63]
[^{225}Ac]-cixutumumab	IGF-1	Mice	Breast cancer SUM149T	0.15 kBq/μg, 8.325, 0.05 kBq, mg/kg and (8 kBq/μg, 8.325 kBq, 2.5 mg/kg)	Extended survival, with a median duration of 122 days, and 2/6 mice had complete tumor mitigation	[64]
[^{225}Ac] Ac-DOTA-anti-VLA-4	α4β1 integrin Cell line B16F10	C57BL/6 male mice Age range (6–8) weeks	Melanoma	In biodistribution (14.8 kBq, 20 μg)	Increased survival with median survival rises 6–8 days. Dose limited hematopoietic toxicity was observed	[65]
[^{225}Ac]-DOTA-MMA	DLL3	NOD SCID female mice. Age range (5–7) weeks	SCLC	296 kBq/kg MTD: 18.8–55.5 kBq	Showed tumor control. In a biodistribution study, this radiolabeled conjugate induced toxicity	[66]
[^{225}Ac] DOTA-Bn	GPA33 antigen	Female athymic nude mice	Colorectal, breast, and neuroblastoma	3.7 MBq	Showed different antitumor efficacy	[67]

Contd...

Table 3: Contd...

Bi-complex	Molecular target	Analysis in	Disease	Dose escalation	Outcome	Reference
^{225}Ac-proteus-DOTA	GPA33 antigen	*In vitro*, *vivo*, biodistribution, therapy	Colorectal, breast, and neuroblastoma	Up to 296 kBq/mouse	Increased overall survival	[68]
[^{225}Ac]-FAPI-04	FAP PANC-1 and MIA PaCa-2 cell line	Male nude mice	Pancreatic cancer	10 kBq, 34 kBq/100 µL	Liver, kidney, and tumor showed high uptake, reduced tumor growth	[69]

DLL3: Delta-like 3 protein, IGF-1: Insulin growth factor receptor 1, PDAC: Pancreatic ductal adenocarcinoma, SCLC: Small cell lung cancer, NOD: Nonobese diabetic, SCID: Severe combined immunodeficiency, PSMA: Prostatic-specific membrane antigen, TTP: Time To Progression, PGLS: 6-phosphogluconolactonase, LNCaP: Lymph Node Carcinoma of the Prostate, U-87 MG: Uppsala 87 Malignant Glioma, HER2: Human Epidermal growth factor Receptor 2, BALB: Bagg Albino, MTD: Maximum Tolerated Dose, PANC-1: Human Pancreatic cancer cell line, FAP: Fibroblast Activation Protein, PaCa-2: Pancreatic Carcinoma-2, PC-3 PIP: Prostate Cancer cell line- Performance Improvement Plan, FVB: Friend leukemia virus B

few antibody reactions like toxicities, fever, chills, and hypotension. Patients with AML who did not respond to or came back after treatment had a poor chance of survival with humanized anti-CD33 therapy.[45] A new study tested ^{225}Ac-lintuzumab, a different kind of Anti-CD33 drug, on 15 people with AML (aged 45-80 years) who had failed or relapsed after previous treatments. Dose level 18.5, 37, 74, 111, or 148 Kbq/kg total (851-14430 KBq) of ^{225}Ac-lintuzumab was received by the oblations without any severe toxicity except myelosuppression and DLT in three patients which lasted for 35 days and died because of sepsis. In a span of four weeks, a decrease in bone marrow blasts was observed in 8 to 12 patients.[46]

Actinium-225-lintuzumab with low-dose cytarabine phases 2 trails

Eighteen patients of age 60 years or older who are not able to endure intensive chemotherapy were treated by ^{225}Ac-lintuzumab together with low-dose cytarabine. 18.5, 37, and 55.5 KBq/kg/fraction with 20 mg BID (twice a day) doses received by patients within phase 1 and 2 trials. Toxicity febrile neutropenia, thrombocytopenia, neutropenia, and pneumonia were seen. In 75% of patients, 68% of them had a reduction in bone marrow blast after one cycle.[47]

Actinium-225-PSMA-617

PSMA (prostatic-specific membrane antigen) constitutes a glycosylated protein situated at the cellular lipid bilayer, and its radioconjugate ^{225}Ac-PSMA-617 is developed using a PSMA inhibitor sequence called glutamate-urea-lysine. This sequence is utilized for renal clearance, and DOTA is employed as a chelating agent in the radioconjugate.[48] 17 patients were medicated by ^{225}Ac-PSMA-617 at Steve Biko Academic Hospital in Pretoria. The treatment has shown a substantial level of effectiveness in therapy, and its tolerability has been enhanced through the reduction of the dosage amount. In 70% of patients, the decrease of prostate-specific antigen (PSA) was 50% and a total of 83% of patients showed PSA decline.[43]

Ongoing Clinical Trails

^{225}Ac is known for its ability to deliver highly localized radiation to cancer cells, thereby minimizing damage to surrounding healthy tissues. The trials listed in table-2 span different medical settings and aim to evaluate the efficacy, safety, and potential applications of ^{225}Ac in treating various types of cancer and other diseases.

Preclinical Perusal

α particles have great potentiality as well as toxicity more than other particles. Consequently, preclinical trials are warranted to investigate the efficacy and to lead to future clinical prospects. A vast amount of preclinical trials have been done till now, and many of them are under observation. A few of them are enlisted [Table 3].

Discussion

Normal vasculature is known as the circulatory system of a human body, where arterioles, veins, and capillaries are distributed at a successively equal distance, while a growing tumor or tumor vasculature can be defined as an unevenly gaped and disorganized system. A solid tumor consists of tumor cells, including immune cells, vasculature, and ECM. Several cell surface and extracellular matrix (ECM) proteins like collagens, elastin, integrins, and glycoproteins are the main reasons for creating tumor vessels by forming progressive supermolecular platforms that further start to grow as new abnormal blood vessels that interrupt oxygen and drug transportation in the tumor cells. These unusual blood vessel enhancements are the major obstacle to radiotherapy and chemotherapy. The highly active and energetic alpha particle-like ^{225}Ac can easily penetrate those immature blood vessels and its suitable geometrical structure terminates tumor neovascular endothelium cells and their originators.[70] The high-linear-energy radiation decayed from alpha particles kills cancer cells while transiting through the blood and lymph systems and also stampedes the network of blood vessels within the tumor by destroying tumor capillary endothelial cells. Cancers like leukemia, lymphoma, and myeloma emerged in the blood. The short-range alpha particles showed an effective outcome that was observed in a phase 1 trial. By manipulating the structure and properties of cell membranes, MABs control tumor growth, while radio conjugates of ^{225}Ac target hormone receptors like estrogen (ER) and androgens, which are more effective in therapy.[71] Nude and transgenic mice have a similar immune system to a human where cancer can generate and are widely used for preclinical studies and many of those radioconjugates came to clinical trial successfully.

Conclusion

Targeted radiotherapy has taken the attention to a fight against cancer worldwide. In a large amount of clinical and preclinical studies, radiochemistry of α emitters has been demonstrated in recent days. Their unique specifications, stability with a chelator, targeting capability to specific cells, cross dose, and bystander effects gave the ability to capitalize on cancer treatment**.** The utilization of ^{225}Ac in TAT shows great potential in the development of novel therapeutic radiopharmaceutical drugs. The remarkable effectiveness of ^{225}AcPSMA-617 in treating prostate cancer has generated substantial international attention and has sparked interest in employing ^{225}Ac as a therapeutic isotope for cancer treatment through TAT. As presented above in this review, we tried to delineate the production, clinical and preclinical studies, and currently ongoing clinical investigation of ^{225}Ac radionuclide. Because of its vast amount of preclinical trials and undergoing clinical investigation in which some of them are completed, ^{225}Ac is considered to be a reliable option for cancer treatment, yet production is an obstacle to overcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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