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Clinical Application of Actinium-225 Radiopharmaceuticals in Targeted Alpha Therapy

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ABSTRACT

Among the vast variety of radionuclides available, a handful of them possess proper features for targeted alpha therapy (TAT). TAT holds the promise of exceeding the effectiveness of conventional radiotherapy methods. Actinium-225 is considered to be an outstanding isotope for TAT in the management of cancer due to its half-life, which enables sustained delivery at the tumor site. This review covers the clinical applications of actinium-225 radiopharmaceuticals.

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Introduction

Targeted therapy has emerged as a significant alternative treatment modality for cancer, complementing traditional approaches such as surgery, chemotherapy, and external beam radiation. Among the Food and Drug Administration (FDA)-approved targeted therapeutics are monoclonal antibodies and small molecules, including tyrosine kinase inhibitors [1]. Additionally, targeted receptor therapy (TRT) is rapidly gaining traction as a valuable class of treatment, offering the unique advantage of delivering therapeutic effects across all cancer sites through selective tumor uptake and retention. This advancement enhances the options available for effective cancer management [2]. TRT uses a specialized targeting vector that shows selective binding and affinity toward tumors. These method provides high retention of radionuclides in tumor or the tumor microenvironment (TME), leading to successful therapeutic results [3].

Antibody platforms, peptides, proteins, and small molecules are frequently used as targeting vectors in TRT and diagnosis [2, 4]. An essential consideration in evaluating the therapeutic potential of vectors is the kinetic profile of the carrier. Generally, vector molecules that exhibit an extended circulation time in the bloodstream demonstrate enhanced tumor accumulation are advantageous for the efficacy of TAT. However, it is important to recognize that prolonged residence time in circulation may lead to an increased radiation dose to healthy tissues. Therefore, the half-life of the radionuclide must align with the plasma half-life of the vector to achieve an optimal tumor-to-background ratio. It is noteworthy that selectivity for radiation-induced damage to malignant tissues may be greater with longer-lived radionuclides, which is advantageous in a therapeutic context while short lived radionuclides are proper for imaging purposes [5-7]. The radionuclides chosen for TRT are primarily those that emit α and β particles, as well as Auger electrons [2, 3, 8].

Alpha Decay for TRT

α-decay is the release of an α-particle, made up of two protons and two neutrons, from the nucleus. This process enables the specific destruction of tumor cells while protecting healthy tissue, due to the restricted penetration depth of α-particles, which ranges from 40 to 80 µm, equivalent to 2 to 10 cell diameters.

An α-particle exhibits a linear energy transfer (LET) of 100 keV/µm, leading to a significant relative biological effect (RBE). The higher LET leads to an increased occurrence of double-strand and clustered DNA breaks, leading to cells being damaged irreparably. As a result, α-emitting radioisotopes display substantial cytotoxicity in both normoxic and hypoxic tumor environments, with the latter generally showing more resistance to radiation treatments based on photons and electrons [9]. Targeted alpha therapy (TAT) emerges as a promising approach in cancer treatment, particularly for tumors with small diameters that exhibit a spatially homogeneous expression of the target molecule. Prior to initiating TAT, it is essential to confirm the adequate expression of the targeted receptor within the malignant tissue. This verification can be achieved through imaging techniques such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), following the administration of a diagnostic counterpart to the therapeutic radiopharmaceutical. Numerous studies have demonstrated favorable therapeutic outcomes associated with TAT.

Actinium-225

Actinium-225 is an alpha-emitting radionuclide that has a half-life of 9.9 days. It undergoes a series of decay processes, resulting in the production of six short-lived radionuclide daughters before reaching a state of near-stable bismuth-209. During the decay, Ac-225 emits a total of four alpha particles, each with energies ranging from 5.8 to 8.4 MeV. These alpha particles can penetrate tissues to a depth of 47 to 85 µm. Additionally, the decay cascade includes two beta disintegrations with energies of 1.6 and 0.6 MeV. Moreover, the disintegrations of francium-221 and bismuth-213 give rise to the emission of gamma rays, which can be utilized for imaging purposes (Figure 1) [10].

Actinium naturally occurs as a result of the radioactive decay of uranium radionuclides. The production of actinium-225 can be achieved through the decay of uranium-233 or the process of neutron transmutation, involving the conversion of radium-226 into actinium-227, and subsequently thorium-228 into thorium-229, via successive capture decay reactions. The primary method employed for the production of actinium-225 has been the radiochemical extraction from thorium-229, which has been in practice since the early 1990s. The acquisition of thorium-229 sources, with a half-life of approximately 7917 years, involves the separation from aged, fissile uranium-233 [11, 12]. Actinium-225 is considered to be an outstanding isotope for TAT in the management of cancer due to its half-life, which enables sustained delivery at the tumor site. The utilization of actinium-225 and its offspring bismuth-213 in labeling molecules

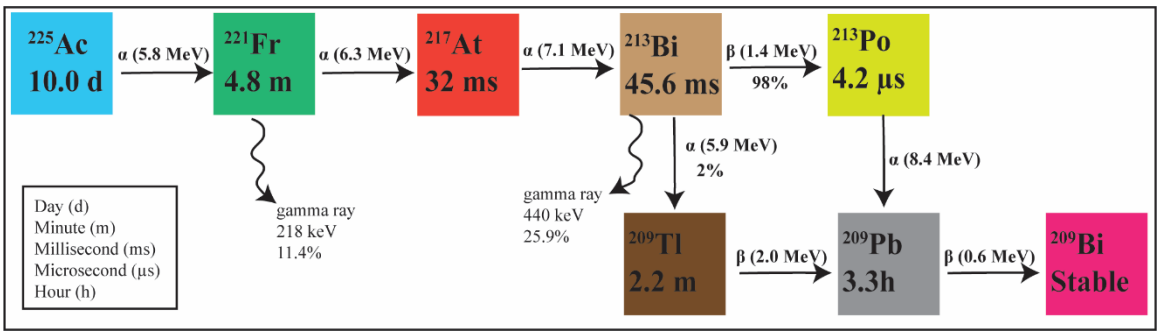

Figure 1. Decay cascade of actinium-225

for TAT is common. Alpha particles typically possess a range of 40-90 μm in tissue, effectively covering the dimensions of a typical vessel within a tumor and concentrating a substantial amount of energy in a localized area, thereby mitigating bystander damage. The emitted alpha particle(s) can induce notable radiation damage owing to their high linear energy transfer; however, their limited range results in lesser harm to the neighboring tissues [13-15]. The progeny of the radionuclide actinium-225 evades and undergo the process of circulation throughout the body, ultimately accumulating in various organs, particularly the kidneys. This accumulation has deleterious effects on healthy organs. Presently, the primary concern lies in the renal toxicity caused by the release of bismuth-213. As a result, there is a consensus to explore alternative approaches, such as employing nano-vehicles, to mitigate the recoil effect of the actinium-225 progeny and enable specific deposition of the radionuclides at predetermined sites [1, 16].

Radiotracers and Clinical Applications

Studies have investigated the clinical application of TAT with different radionuclides for the treatment of various cancers including prostatic cancer, neuroendocrine tumors, hematologic malignancies and glioblastoma. From these cancers, prostatic cancer has been more studied and most of these clinical studies, have investigated the therapeutic efficiency of the [^{225}Ac]Ac-DOTA-PSMA in metastatic castration-resistant prostate cancer (mCRPC) patients.

There are some reports of great therapeutic response following treatment with actinium-225 based alpha radioimmunotherapy in mCRPC patients resistant to both conventional therapies and ^{177}Lu-based radioimmunotherapy. Some studies have reported cancer progression and appearance of new metastatic lesions despite initial clinical and biochemical response following a four cycle of [^{225}Ac]Ac-DOTA-PSMA in a mCRPC patient [17]. The first clinical experience with [^{225}Ac]Ac-DOTA-PSMA-617 reported significant radiological and biochemical response in two prostatic cancer patients who had been heavily treated prior to alpha-radioimmunotherapy [18]. All the clinical studies on [^{225}Ac]Ac-DOTA-PSMA-617 are listed in Table 1 with details.

Some studies evaluated the feasibility of actinium-225 labeled substance-P ([^{225}Ac]Ac-DOTA-SP) for the treatment of glioblastoma. [^{225}Ac]Ac-DOTA-SP was injected through a catheter-port system for the local delivery of the treatment to the tumor. PET/CT scans using [^{68}Ga]Ga-DOTA-SP, coinjected with [^{225}Ac]Ac-DOTA-SP, was performed for the assessment of the tumor delivery of the treatment and revealed high uptake at the tumor site and in most cases, with less than 3% and 1% of injected activity accumulated in the blood pool and bladder, respectively. For assessment of the treatment related toxicity, blood cell counts, kidney function tests and liver enzymes were measured. No new-onset epilepsy or focal neurological symptoms was noted following treatment [19].

Other studies reported remarkable disease control and radiological response following [^{225}Ac]Ac-DOTA-TATE therapy. To that end, all patients had clinical response with improvement in quality of life and displayed no significant toxicity and change in laboratory parameters. Some of the patients experienced gastrointestinal symptoms like nausea which were related to concurrent amino-acid infusion [20].

Recently, the promising therapeutic results have obtained with [^{225}Ac]Ac-DOTA-lintuzumab targeting CD33-positive cells in patients with refractory or relapsed acute myeloid leukemia. In this study, the patients exhibited reduction in peripheral blood blasts and bone marrow blasts, respectively. The maximum tolerated dose determined to be 111 kBq/kg, as the highest dose of 148 kBq/kg led to significant marrow toxicity [21]. All the clinical studies are mentioned in Table 1.

Table 1. Overview of human studies with Actinium-225

Radiotracer	Main Findings	Toxicities	Ref.
[^{225}Ac]Ac-DOTA-SP	A suitable choice for recurrent glioblastoma therapy.	No significant liver, kidney, and hematological toxicity.	[19]
[^{225}Ac]Ac-DOTA-TATE	Significant improvement in all scores of ECOG, KPS, and analgesic score. Significant improvement of QLQ-H&N35 scores in head & neck paraganglioma patients. No patient experienced complete remission.	No hepatological, renal, and grade III/IV hematological toxicities.	[20]
	Increased tumor uptake with 7 MBq of [^{225}Ac]Ac-DOTA-TATE	No significant side effect.	[22]
	Favorable uptake in mass lesions. Favorable potential choice for cases with prior resistant to [^{177}Lu]Lu-DOTA-TATE.	No significant toxicity.	[23]
	Improvement of life quality. Significant decrease in symptom. No significant alteration in the sexual function and social function. No significant reduction of chromogranin level after therapy.	Significant decrease in gastrointestinal symptoms. Low toxicity profile in the short-term follow-up.	[24]
	Strong SSTR2 expression identified by PET/CT in 30% of patients. Evaluation of treatment efficacy in patients led to near complete response.	No side effect.	[25]
[^{225}Ac]Ac-DOTA-PSMA-617	Slowing down disease progression.	No significant side effect.	[17]
	Significant improvement in functional and biochemical response. Decrease serum level of PSA level following the second cycle therapy.	No significant side effect.	[26]
	Long-lasting complete remission by 3 cycles of ^{225}Ac-PSMA-617 Decreased PSA level below the limit range.	Increased creatinine level. Chronic xerostomia.	[27]
	No treatment response. Both patients died owing to cancer progression.	Both cases with prior CKD developed progressive CKD.	[28]
	Complete imaging response in both patients. Patients experienced a PSA decline below measurable.	Xerostomia No relevant hematological toxicity.	[18]
	Remarkable antitumor activity evidenced by tumor marker decline. Objective radiologic response in 80% of the patients. Insufficient antitumor response without toxicity with a treatment activity of 50 kBq/kg. A balanced trade-off between toxicity and biochemical response with a treatment activity of 100 kBq/kg repeated every 8 weeks.	Dose-limiting toxicity (severe xerostomia).	[29]
	PSA declines in patients. Median tumor control duration was 9 months under last-line therapy. Five patients had sustained responses for more than two years.	Xerostomia	[30]
	PSA decline >90% reported in 82% of patients. 41% of patients showed undetectable serum PSA after 12 months treatment. Reducing the administered activities in subsequent treatment cycles resulted in decreased toxicity to salivary glands. A > 50% decrease in lesions avidity was seen in patients.	Grade 1/2 xerostomia reported in all patients.	[31]
	PSA decline >50% reported in 70% of patients. PSA reduction observed in 83% of patients.	Xerostomia reported in 85% of patients. Anemia reported in 38.5% of patients. Renal failure grade III-IV in patients with history of renal impairment.	[32]
	PSA decline >50% reported in 65% of patients.	Grade 1/2 xerostomia reported in all patients, and discontinuation occurred in number of patients. One-third of patients experienced grade 3/4 hematological toxicity.	[33]

Radiotracer	Main Findings	Toxicities	Ref.
[^{225}Ac]Ac-DOTA-PSMA-617	PSA decline >50% reported in 65% of patients. Utilizing low-activity ^{225}Ac-PSMA-617 / full-activity ^{177}Lu-PSMA-617 in a single course of tandem therapy increased the response to therapy.	Grade 1 and 2 xerostomia reported in 40% and 25% of patients.	[34]
	PSA decline >50% reported in 46% of patients. Significant improvements in the disease-related symptoms. A notable improvement reported in pain levels, difficulties with urination, bone discomfort, fatigue, and limitations in physical activity.	No notable alterations were observed in the subscore for treatment side effects.	[35]
	PSA declines ≥50% and ≥90% reported in 69% and 46% of patients. More than 90% decrease in total tumor volume was seen in all patients. A clinically significant reduction in pain. Improvement in quality of life.	Persisted xerostomia observed during follow-up.	[36]
	Significant efficacy reported by tandem therapy of [^{225}Ac]Ac-PSMA-617 and [^{177}Lu]Lu-PSMA-617 for mCRPC patients. Stable disease, partial remission, disease progression reported in 41.2%, 29.4%, and 29.4% of patients. Better survival reported among patients experienced partial remission. Except discordant in 29.4% of cases, high levels of concordance were demonstrated in molecular imaging responses and biochemical PSA responses. Molecular imaging response demonstrated a greater estimation value for survival outcomes following tandem therapy than changes in PSA levels.	Well-tolerated.	[37]
	Resolution of all symptoms after 7 weeks of follow-up Decrease in PSA level by 99% after treatment. A notable decrease in the size and avidity of all metastatic lesions.	Mild xerostomia. No significant toxicity.	[38]
	Both the parotid and submandibular glands were impacted by radiation exposure. Sialendoscopy, combined with dilatation, and steroid injection, demonstrated significant improvements in salivary gland function.	No complications took place after sialendoscopy.	[39]
	Favorable anti-tumor effect among 80% of patients. Significant risk factors for hematologic toxicity related to [^{225}Ac]Ac-PSMA-617 included the number of treatment cycles, renal dysfunction, and age. PSA response reported in 80.2% of patients.	Severe hematologic toxicity rarely occurred.	[40]
	PSA decline >50% reported in 91% of patients. PSA response observed in 96% of patients. Increased estimated median survival.	Grade I–II xerostomia was seen in 81% of patients. Grade III–IV nephrotoxicity reported in 3 patients.	[41]
	Increased estimated median survival. Significant improvement in QOL Symptom score, including fatigue, pain, constipation, and insomnia.	Xerostomia was the most common side effect.	[42]
	PSA decline >50% reported in 50% of patients. PSA response observed in 75% of patients. Increased estimated median survival.	No significant difference between the pre- and post-treatment conditions in terms of side effects.	[43]
[^{225}Ac]Ac-DOTA--PSMA-I&T	PSA decline >50% reported in 50% of patients. PSA response observed in 79% of patients.	No acute toxicity. The main toxicity was grade 1-2 xerostomia.	[44]
	The α-targeted response achieved by two cycles of ^{225}Ac-PSMA-I&T.	Grade 2 xerostomia No grade 3/4 hematological side effects.	[45]
[^{225}Ac]Ac-DOTA-TOC	Partial remission by one cycle of ^{225}Ac-DOTATOC therapy after failure of β-emitter PRRT with ^{90}Y and ^{177}Lu. Significant lower lesions after 3 months.	Well-tolerated.	[46]
	Administering 20 MBq per cycle, with a repetition every four months, and cumulative doses reaching 60–80 MBq is considered reasonable. Pre-existing renal risk factors significantly contribute to the likelihood of treatment-related kidney failure.	Dose-dependent acute hematological toxicity.	[47]

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this review article.

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Authors contribution's

Conceptualization, methodology, investigation, resources review and editing: All authors; Writing the original draft, and supervision: Sajjad Molavipordanjani.

Conflict of interest

The authors declared no conflict of interest.

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