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LETTER TO THE EDITOR

Production of the state of the art therapeutic radiopharmaceuticals in Iran, from beta- to alpha-emitting targeted radionuclide therapy: Clinical advances and perspectives

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Dear Sir,

Iran has had many achievements in recent years in producing different diagnostic and therapeutic radiopharmaceuticals [1]. Presence of over 210 nuclear medicine centers and abundant human resources comprising nuclear medicine physicians, radiopharmacists, physicists and related technologists in the country has established a resilient foundation and capability for progressing both basic and clinical nuclear medicine sciences and facilities [1]. In addition to the presence of beta-emitting radioisotopes, the recent domestic manufacturing by Pars Isotope Company and access to therapeutic alpha-emitting radiopharmaceuticals such as $^{223}RaCl_2$, [^{225}Ac]Ac-PSMA-617 and [^{225}Ac]Ac–DOTATATE have unveiled promising prospects in the realm of targeted radionuclide therapy (TRT) in Iran.

TRT alternatively referred to as molecular radiotherapy, targeted radiotherapy, or radiotheranostics, is a rapidly advancing field that has recently achieved significant breakthroughs [2, 3]. TRT involves the personalized selection of patients by employing molecular imaging techniques to verify the presence of a specific biological target on the surface of cancer cells or within the vascular

and/or stromal components of metastatic sites. Currently, the only approved alpha-emitting radiopharmaceutical is Xofigo ($^{223}RaCl_2$), which received approval in 2013. However, the approvals of beta-emitting [^{177}Lu]Lu-PSMA-617 (Pluctivo, approved in 2022) for the treatment of metastatic castration-resistant prostate cancer (mCRPC) expressing prostate-specific membrane antigen (PSMA), and [^{177}Lu]Lu-DOTATATE (Lutathera), approved by FDA in 2018) for therapy of somatostatin receptor-positive neuroendocrine tumors (NETs), will significantly elevate TRT to the forefront of cancer treatment. Nonetheless, certain patients either do not respond to or develop resistance to ^{177}Lu-based therapies, even when the target proteins are adequately expressed on the surface of cancer cells [4, 5]. The targeted alpha therapy (TAT) approach is currently under active exploration in numerous preclinical studies and a few early clinical studies, with the use of radionuclides such as ^{225}Ac, ^{213}Bi, ^{211}At, ^{227}Th, and ^{212}Pb. Among these investigations, studies involving ^{225}Ac are more extensive and dynamic, showing promising results [6]. These radiopharmaceuticals possess unique physical properties, such as high linear energy transfer (LET) and a short range in tissue relative to beta emissions, enabling them to directly kill hypoxic or radio- and chemo-resistant cancer cells.

Pierre and Marie Curie, along with Alexander Graham Bell, conducted research on cancer-TAT in the early 1900s [7]. α-particle emitters have significant curative effects, targeting small clusters of metastatic cancer cells with minimal damage to normal tissues. They provide a therapeutic option for patients resistant to other treatments [8]. The high LET of α emitters causes efficient cell destruction through DNA damage and reactive oxygen species (ROS) production [9]. Additionally, this therapy may lead to the decrease of primary tumors and other cancerous lesions through "the abscopal effect," possibly involving the immune system [10, 11].

In the last decades several α-particle emitters had been studied including Actinium-225 (^{225}Ac). Clinical applications of TAT primarily involve the use of ^{225}Ac and its daughter nuclide ^{213}Bi [12]. The potential for SPECT imaging and theranostic nuclear medicine applications has generated increasing interest in using ^{225}Ac. However, limited worldwide accessibility and practical production techniques, involving controlled nuclear materials and highly irradiating radioactive accelerator targets, have hindered substantial clinical investigations and widespread use in human patients [13].

^{225}Ac is a radioactive element with a long half-life of 9.9 days. It is part of the "neptunium series" and its decay series includes six short-lived radionuclide daughters, ending with ^{209}Pb. The cascade includes emissions of α particles, β− particles, and γ radiation [14].

In recent years, various beta emitters like ^{177}Lu and ^{90}Y, labeled with different somatostatin receptors (SSTR) analogues and PSMA targeted agents, have been introduced for treating neuroendocrine tumors (NETs) and metastatic prostate cancer with low toxicities [15-25]. Despite their advantages, a major limitation of these theranostic agents is that 26-55% of patients only showed stable disease and 18-32% showed refractory or progressive disease after treatment [22, 24, 26]. Since a significant number of patients did not respond to therapy with beta emitters, the theoretical physical advantages of alpha emitters over beta emitters provide a lasting option to further improve the efficacy of PRRT by labeling the peptides with alpha-particle emitters [27].

Studies conducted on ^{225}Ac have demonstrated its potential in the treatment of NETs and metastatic prostate cancer. Furthermore, additional radiopharmaceuticals are currently under development for various other types of cancer [28-30]. There are several strategies have been discussed in using alpha and beta emitters. The first strategy is using a carrier labeled with either a beta or alpha emitter for therapy in patients with castration-resistant prostate cancer. Alpha therapy has shown high effectiveness in patients who have failed ^{177}Lu therapy or have disseminated bone marrow disease [4]. A dosimetric analysis suggests that a treatment activity of 100kBq/kg ^{225}Ac every 8 weeks is a reasonable balance between toxicity and response [31]. The second strategy is using a cocktail of a carrier molecule labeled with both a beta and alpha emitter. It is unclear if this strategy is better than using only one isotope. Another approach is using two different carriers targeting different tumor subpopulations, with the beta-labeled carrier for debulking large tumor masses and the alpha-labeled carrier for targeting critical subpopulations such as stem cell-like cells [32].

Several studies have been conducted to assess the feasibility of ^{225}Ac-labeled PSMA-targeted agents for treating patients with prostate cancer [4, 28, 30, 33, 34]. Ballal et al. evaluated the efficacy of [^{225}Ac]Ac-PSMA-617 in patients with

metastatic castration-resistant prostate cancer (mCRPC) who had exhausted all standard treatment options. They indicated any PSA decline in 91% and more 50%. In addition, the TAT was found to be well-tolerated with acceptable adverse events and effective in treating patients with end-stage mCRPC [33]. Ma et al. conducted a Systematic Review and Meta-Analysis to assess the efficacy and safety of [^{225}Ac]Ac-PSMA-617 in treating mCRPC patients. The final analysis included 6 retrospective studies with a total of 201 patients. The results showed that 87.0% of patients experienced decreased PSA levels and 66.1% experienced a decrease of more than 50%. The researchers concluded that [^{225}Ac]Ac-PSMA-617 is a safe and effective treatment for mCRPC patients, with low toxicity [34]. However, the shortage of ^{225}Ac remains a challenge and hinders the evaluation of ^{225}Ac-TAT in large-scale studies.

Another promising therapeutic option for metastatic mCRPC involves the use of $^{223}RaCl_2$, also known as Alpharadin or Xofigo, has significantly impacted the field of alpha-radiation therapy, with 52 clinical trials registered on clinicaltrials.gov. The majority of these trials (80%) focus on prostate cancer, and a significant portion (35%) involve a combination of drugs with $^{223}RaCl_2$. One notable phase III trial called ALSYMPCA demonstrated the efficacy and safety of $^{223}RaCl_2$ compared to placebo in symptomatic mCRPC patients. The trial showed that patients receiving $^{223}RaCl_2$ had a significantly longer overall survival (14.9 months) compared to those on placebo (11.3 months). These positive results led to the approval of $^{223}RaCl_2$ by the Food and Drug Administration for the treatment of mCRPC in May 2013. Additionally, $^{223}RaCl_2$ has shown the ability to delay the increase in certain disease markers and has been well-tolerated by patients, leading to an improvement in their quality of life. However, it should be noted that $^{223}RaCl_2$ does not target soft-tissue disease or the circulating component of the disease [35, 36].

Furthermore, various SSTR analogues labeled with ^{225}Ac had been introduced for treatment of NET [5, 29, 37]. The first study in use of alpha-PRRT with [^{225}Ac]Ac–DOTATOC in humans was in October 2018. Ten patients with metastatic NETs that had progressed after [^{90}Y]Y– and/or [^{177}Lu]Lu–DOTATOC therapy received intra-arterial [^{225}Ac]Ac–DOTATOC (~8 MBq). The treatment was generally well-tolerated and showed effectiveness, indicating its potential as a potential therapeutic option for advanced NETs that are resistant to β-PRRT [36]. A prospective study was conducted on 91 patients with inoperable or metastatic SSTR-expressing GEP NET to explore the long-term outcomes of [^{225}Ac]Ac–DOTATATE. Patients were categorized into three groups depending on their pretreatment with ^{177}Lu-PRRT: prior ^{177}Lu-PRRT refractory group, prior ^{177}Lu-PRRT disease control group, and ^{177}Lu-PRRT naïve group. After a median follow-up duration of 24 months, the median OS was not attained at the time of analysis; thus, a 24-month survival probability of 70.8% was calculated. Bone metastases, a cumulative dose of [^{225}Ac]Ac–DOTATATE < 37 MBq and PD with [^{225}Ac]Ac–DOTATATE were associated with significantly poorer OS. The presence of bone metastases, a cumulative dose of [^{225}Ac]Ac–DOTATATE < 37 MBq and PD with [^{225}Ac]Ac–DOTATATE were also associated with a significantly reduced PFS. Only 2 of the 79 evaluable patients achieved a complete response. There were 38 partial responses, 23 stable diseases and 16 progressive diseases [5].

It should be mentioned that when utilizing alpha emitters in a clinical setting, specific measures need to be taken regarding imaging, dosimetry, and radiation protection, which differ from those employed for beta emitters. The dosimetry poses particular challenges due to the exceptionally short range and extremely high LET of alpha particles. As $^{223}RaCl_2$ is now being used globally, most of the available data is based on this radionuclide and can be extrapolated to other therapies involving alpha emitters. During the administration of radioactive materials, it is essential to have consistent surveying practices, appropriate radiation instrumentation, and effective decontamination methods in place. Because of the unique characteristics of alpha emitters, there are specific considerations for radiation protection in TAT. Alpha particles cannot pass through many gas-filled detector windows (e.g., geiger-Müller [gM] detectors), but beta and gamma particles emitted within an alpha decay chain can be detected. Detectors optimized for alpha particle detection, such as Zinc Sulphide scintillators, filter out beta particles or photons, leading to a lower minimal detectable activity [38]. During the administration of [^{225}Ac]Ac-PSMA-617 produced by (Pars Isotope Company, Iran), we use the LB 124 SCINT Series Contamination Monitors, which operate on scintillation technology. These instruments are employed to detect radioactive alpha and beta-gamma contaminations on various surfaces, including floors, walls, desks, objects, clothing, and skin. One of their

advantages is the ability to measure alpha and beta-gamma contaminations simultaneously and separately, while also providing measurements of gamma dose rate. A risk assessment should be conducted before preparing or administering new radiopharmaceuticals, following IAEA GSR Part 4 [39]. It should cover risks to staff, the public, and patients, including dose limits and constraints. Control measures should be based on these assessments to minimize exposure and mitigate incidents. Work areas should be designed to minimize exposure, and foreseeable incidents should be identified. Literature on radiation protection for alpha emitting radionuclides is limited, with more work needed for other radiotherapeutics. Careful examination of decay chains and manufacturing processes for alpha emitting radionuclides is crucial, as they can have different associated emissions and long-lived progeny or impurities which impact radiation safety. Occupational exposure is generally low, but precautions are needed to avoid skin contamination, inhalation, and ingestion. Personalized risk assessments for patients, considerations for extravasation, and examination of biokinetics and progeny translocation are important for radiation protection in treatment. Risk assessments should cover patient death and steps for minimizing risks when starting a new radionuclide service [40].

It is important to exercise caution during administration to prevent any spills on the skin of both the patient and the staff. Accidental needle sticks and skin exposure to radioactive substances during treatments are classified as significant occurrences and require immediate and appropriate attention due to the potential absorption of radioactive material. Swift cleansing of the affected area and continuous monitoring are vital measures in handling these incidents. When there is a suspicion of radioactive material intake in specific monitoring scenarios, the assessment and response should align with the potential level of risk involved. Adherence to established protocols and guidelines for the handling and management of such incidents is essential to guarantee the safety of both patients and healthcare providers. We have prepared a card that contains radiation safety precautions for patients undergoing alpha-emitting therapies. Patients are required to carry this card with them at all times for one month following each injection.

In total, the utilization of alpha-emitting radionuclides for cancer treatment has sparked significant interest due to their heightened radiotoxicity per unit of administered activity compared to radionuclides that emit beta, gamma, or X-rays. With the implementation of robust administrative and engineering controls, alpha-emitting radionuclides can be safely handled and administered in clinical settings. It is of utmost importance to have suitable personal protective equipment, training techniques, and radiation detection instrumentation in place to minimize contamination incidents and ensure the safety of both clinical staff and the general public. Patient release instructions for alpha-emitters primarily focus on hygiene precautions, aiming to prevent accidental inhalation or ingestion of radioactive material by others. Given their multitude of benefits, alpha-emitting radionuclide therapy is poised to become a significant strategy in the arsenal of cancer management in the coming years.

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