Lutetium-177 compared to emerging radionuclides in Prostate-Specific Membrane Antigen Castration-Resistant Prostate Cancer (PSMA-mCRPC)

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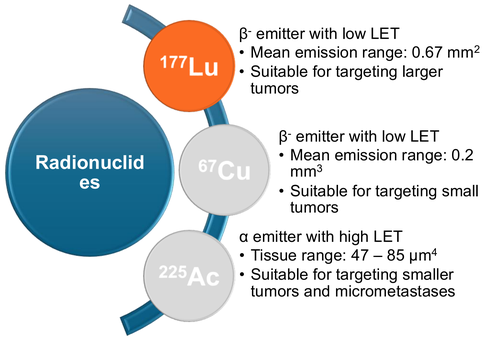
Background

- Lutetium-177 vipivotide tetraxetan (^{177}Lu-PSMA-617) is the only radioligand therapy (RLT) approved for treating adult patients with PSMA-mCRPC who no longer respond to hormone deprivation.
  - The PSMA targeting ligand or tracer, PSMA-617, is chemically attached to the therapeutic radionuclide ^{177}Lu, which releases energetic beta particles to provide precise cell-killing radiation to the disease site.
- The VISION trial, a pivotal phase III study, demonstrated that ^{177}Lu-PSMA-617 significantly prolonged overall survival (OS) and progression-free survival (PFS) in patients with PSMA-mCRPC.[1]
- This breakthrough established ^{177}Lu-PSMA-617 as a standard in RLT care, setting a benchmark for alternative radionuclides like Copper-67 (^{67}Cu) and Actinium-225 (^{225}Ac), which are currently being explored for their potential benefits in prostate cancer treatment.



*Linear energy transfer (LET): describes the energy deposition density and determines the biological consequence of radiation exposure.[2]

Objectives

- Summarize the radioactive and pharmacokinetic differences between ^{177}Lu, ^{67}Cu, and ^{225}Ac.
- Discuss how the differences in the chemical properties of the radionuclides translate to clinical applications in treating patients with PSMA-mCRPC.
- Relate the significance of the current landscape of radionuclide production and the feasibility of mass clinical usage.

Justification / Documentation

Radionuclide pharmacokinetics / pharmacodynamics

^{177}Lu				
Distributes to gastrointestinal tract, liver, lungs, kidneys, heart wall, bone marrow, and salivary glands[2]	Renal clearance is fast (1.7 ± 0.8 h), then slowed (41.1 ± 9.3 h)[2]	Radioactive half-life of 6.64 days[2]	Single-strand DNA breaks over extended time, with limited effects on neighboring healthy tissue[2]	γ rays during decay enables single photon emission computed tomography (SPECT) imaging[2]
^{67}Cu				
Evidence of some nonspecific liver and bowel uptake; chelator minimizes liver accumulation[3]	Primary hepatobiliary excretion; renal clearance dependent on chelator used[3]	Shorter radioactive half-life of 2.58 days[3]	Higher dose rate and faster tumor response[3]	Also emits low-energy γ rays, offering use for SPECT imaging and scintigraphy[3]
^{225}Ac				
Primary hepatobiliary clearance, with some renal excretion[5]	Radioactive half-life of 9.9 days[4]	Highly cytotoxic double-strand DNA breaks[5]	Also emits low-energy γ rays, offering use for SPECT imaging and scintigraphy[4]	

- Multicenter, single-arm, dose-escalation trial with cohort expansion phase I/IIa clinical trial to determine the safety and efficacy of ^{67}Cu-SAR-bisPSMA in patients with PSMA-mCRPC.[6]
- Preliminary data shows favorable safety profile (including no Dose Limiting Toxicity), and significant reductions in PSA level.[6]
- Recently granted Fast Track Designation in February 2025 by the U.S. Food and Drug Administration.[6]

SECuRE – ^{67}Cu-SAR-bisPSMA

- International, open-label, dose-escalation phase I trial to determine the safety and efficacy of ^{225}Ac-PSMA-617 in patients with PSMA-mCRPC.[7]
- ^{225}Ac has been developed as additional option to patients refractory to theranostics with β- emitters.[4]
- In a study involving 53 mCRPC patients, ^{225}Ac shows promise in significantly reducing PSA levels (50% decline) and extending OS and PFS.[8]

AcTION – ^{225}Ac-PSMA-617

- The international, open-label, phase III clinical trial VISION evaluated ^{177}Lu-PSMA-617 in patients with PSMA-mCRPC previously treated with at least one androgen deprivation therapy and taxane-based regimen.[1]
- Results from the trial exhibited prolonged imaging-based OS (15.3 months vs. 11.3 months) and PFS (8.7 months vs. 3.4 months) for patients on ^{177}Lu-PSMA-617 combined with standard care, compared with standard care alone.[1]

VISION – ^{177}Lu-PSMA-617

Adaptability

- ^{177}Lu is primarily produced from ^{176}Lu by nuclear fission reactor to give carrier-added (c.a.) ^{177}Lu.[2]
  - An indirect route from irradiating ytterbium-176, by nuclear fission reactor can produce no-carrier-added (n.c.a.) ^{177}Lu.[2]
  - Generally, non carrier added (n.c.a) ^{177}Lu is far more effective, easier to administer, and preferred for production.[2]
  - Rising demands of n.c.a. ^{177}Lu and the current political situation in Russia could result in limited availability and rising cost.[2]
- ^{67}Cu is produced from irradiating zinc-70 in a cyclotron.[9]
  - It is only available in the United States through the Department of Energy Isotope Program (DOE-IP).[9]
  - The limited availability of ^{67}Cu in clinically suitable quantities and quality has emerged as a significant barrier to its broader application.[9]
- ^{225}Ac is mainly produced from the parent isotope thorium-229.[3]
  - Alternative production is possible via thorium-232 through proton linear accelerators and irradiation of radium-226.[3]
  - As seen with ^{67}Cu, production is supply limited, and only available in the United States through DOE-IP.[3]

Significance

- RLTs offer a significant boost in advanced-stage prostate cancer treatment, backed by efficacy and safety data seen in the VISION study.
- With the only FDA-approved RLT treatment for prostate cancer in ^{177}Lu-PSMA-617, ongoing research with alternative radionuclides offer opportunities to refine the efficacy and safety of the modality.
  - Conducting extended 177Lu-PSMA-617 treatment cycles.
  - Alternating between α and β- emitters at lower doses, targeting different tumors.
  - Including patients without extensive prior prostate cancer treatment.
- As clinical trial data emerges and advancements in radionuclide production methods potentially improves, additional opportunities may become available for patients with PSMA-mCRPC and those expressing other tumor types.

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Disclosure

Marvellous Olowookere (olowookere.1@osu.edu): Nothing to disclose

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