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Comparison of promising new short range therapeutic radiopharmaceuticals using 225Ac, 213Bi and 161Tb

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Prostate-specific membrane antigen is a prominent imaging biomarker in nuclear medicine. With Gallium-68 (68Ga) opportunely available to hospital radiopharmacies we recently developed a PSMA11 single kit vial radiolabeling solution which is now routinely used in the Steve Biko Academic hospital in Pretoria, South Africa. The most widely used therapeutic pendant for 68Ga is 177Lu but recent advances in radionuclide production methods have made 225Ac, Bi213 and 161Tb available as alternatives to 177Lu. This created interesting opportunities to treat metastases with the short range Alpha or Auger and conversion electron emissions.
225Ac is a very promising radionuclide for targeted alpha therapy. With its relatively long half-life (9.9 d) it has enough time to target also less-easily accessible tumours, and the 4 emitted alpha's in the decay chain ensure effective cell killing once at the targeted site. 225Ac is produced by radiochemical extraction from 229Th at the Institute for Transuranium Elements, Karlsruhe, Germany. In a recent study by the Sathekge group in Pretoria, [225Ac]Ac-PSMA-617 radioligand therapy of chemotherapy-naïve patients with advanced metastatic prostate carcinoma led to a ≥ 90% decline in serum PSA in 82% of patients including 41% of patients with undetectable serum PSA who remained in remission 12 months after therapy.

In contrast the radioactive decay of 213Bi (T½= 46 min) results in the emission of two high-LET α-particles releasing around 100 keV/μm. Due to the relatively short half-life of 213Bi, it can deliver a high radiation dose to the target within a short period of time. 213Bi is eluted from 225Ac/213Bi Generator (ITG, Munich, Germany). In a recent study by the Sathekge group in Pretoria a first-in-human treatment with [213Bi]Bi-PSMA-617 in a patient with mCRPC that was progressive under conventional therapy, was undertaken. The patient was treated with two cycles of [213Bi]Bi-PSMA-617 and restaging with [68Ga]Ga-PSMA PET/CT after 11 months showed a remarkable response w.r.t. soft tissue metastases.

The use of these short range emitters does not go without challenges that will have to be overcome. Upon emission of an alpha particle, the daughter nuclide experiences a recoil energy which is several orders of magnitude larger than the energy of the chemical bond of the nuclide resulting in the daughter to be released from the targeting vector.
Terbium is a unique element, as it provides a quadruplet of radionuclides suited for diagnostics and therapy in nuclear medicine. 161Tb (Auger/conversion electron and β−emitter, T1/2 = 6.9 d) was produced by neutron irradiation of enriched 160Gd in the SAFARI-1 research reactor from which no-carrier-added 161Tb was produced. In a recent study by the Müller group in Villigen-PSI, [161Tb]Tb-PSMA-617 showed superior in vitro and preclinical in vivo results as compared to [177Lu]Lu-PSMA-617 confirming theoretical dose calculations with regard to a positive effect of conversion and Auger electrons.
The various options & pros and cons for these three radionuclides/radiopharmaceuticals will be discussed.

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