Journal of Nuclear Medicine, published on September 21, 2017 as doi:10.2967/jnumed.117.198333

More alpha than beta for prostate cancer?

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Short running title: PSMA alpha

Article category: Hot topic

Radionuclide therapy for prostate cancer started more than 70 years ago (*1*). Nuclear medicine has since then evolved considerably to provide a multitude of new imaging and therapy options. The past decade witnessed unprecedented expansion of radioligands for prostate cancer. Milestones include the first alpha emitter for treatment of symptomatic bone metastases (*2*) and theranostic vectors directed at the prostate specific membrane antigen (PSMA) or Bombesin receptor (*3,4,5*). However current radionuclide therapies are applied at a late stage of the disease aiming at palliation. Despite recent advances for treatment of metastatic prostate cancer, cure remains an unmet need of the 21st century. Cancer spreads early and develops slowly as sub-millimeter occult lesions. Lesions grow at distant sites and become detectable only when significant morphologic or metabolic alterations have formed, often years to decades after the initial spread (*6*). Effective ablation of small metastases is critical for cure, and presents a specific challenge for beta-emitting radionuclide therapy. Millimeter range beta particles deliver insufficient amounts of radiation to millimeter size tumor lesions, as energy deposition extends and dilutes beyond lesion boundaries (Figure 1). Alpha radiation, due to its µm range, targets millimeter size tumor volumes at higher relative yield (Figure 1). Further evidence points to a superior biological effectiveness for alpha therapy based on high linear energy transfer resulting in frequent double-stranded DNA breaks (*7*). However are basic advantages of alpha therapy associated with a clinical benefit?

^{223}Ra was the first alpha-emitter, approved for survival benefit in patients with symptomatic bone-metastatic castration resistant prostate cancer (mCRPC) (*2*). ^{223}Ra therapy comes with a low rate of serious adverse events (*2*) thought to be based on sparing of healthy red marrow by the short range alpha particles. On the contrary beta emitting bone-seeking ^{153}Sm and ^{89}Sr effectively reduce bone pain, however without evidence for survival benefit and at higher rates for hematologic toxicity (*8,9*).

^{223}Ra alpha therapy has become an important option in the management of mCRPC. However bone-targeting is of limited value in patients with extra-osseous disease (*10*). Effective targeting

of skeletal and extra-skeletal disease is achieved by *i.v.* administration of radio-labeled small ligands for the prostate-specific membrane antigen (PSMA) (*11*). ^{177}Lu-labeled PSMA617 induced a PSA drop of more then 50% in about half of mCRPC patients with bone, lymph node and/or soft tissue metastases (*12*). Significant tumor shrinkage occurred and, in a few patients even complete response was achieved after PSMA-directed radioligand therapy (*12,13,14*). However disease inevitably recurs. Kratochwil and colleagues were able to salvage 9 of 11 patients with ^{177}Lu-PSMA617 recurrent mCRPC by switching to ^{225}Ac-PSMA617 alpha therapy (*15*). A high response rate was achieved by repeat application of 100 kBq/kg ^{225}Ac-PSMA617, an alpha therapy protocol with acceptable toxicity for salivary glands (*15*).

Preclinical and clinical evidence indicates higher efficacy for alpha- versus beta-based therapy of prostate cancer. Thus, alpha therapy should be in the focus of research aimed at cure of metastatic disease. Several challenges need to be overcome for improved effectiveness and broad clinical implementation: a) a reliable, high-yield, pharmaceutical-grade supply of alpha-emitter, must be established to enable clinical trials and subsequent wide spread distribution. For ^{225}Ac, the current annual global supply estimated at 1.2-1.7 Ci would treat less than 2000 patients with four cycles ^{225}Ac-PSMA617. Supply comes nowhere near meeting the estimated demand of 50 Ci listed in the 2008 US Department of Energy report (*16*). Several alternative production methods were evaluated, including low energy proton irradiation of ^{226}Ra (*17*) and high energy proton irradiation of ^{232}Th (*18*) in a cyclotron. However, chemical processing and large scale production methods are still under development. b) Prospective, multicenter clinical trials need to be conducted. Recently, NETTER-1 and ALSYMPCA established new radionuclide therapies by reporting improved progression-free and overall survival (*2,19*). Both studies may serve as a role model for future trial designs aimed at approval and reimbursement of alpha therapy. c) Given the favorable safety of ^{223}Ra and ^{225}Ac-PSMA617, alpha therapy should be performed at an earlier stage of the disease. Combination of surgery, adjuvant radionuclide therapy and hormonal therapy has the potential to cure metastatic disease, a key lesson learned

almost one century ago from the application of radioiodine in patients with differentiated thyroid cancer (*20*). Likewise, adjuvant PSMA-directed alpha therapy may cure, when performed early and in conjunction with other systemic treatment. d) Alpha therapy should be evaluated in combination with potentially synergistic pharmacologic approaches. Alpha radiation induces replication stress, characterized by the accumulation of double-strand DNA breaks (*21*). Small-molecule inhibitors of double-strand DNA break repair pathways demonstrated anti-tumor properties in pre-clinical models and are being investigated in over 50 active clinical trials (*22*). Combination of PSMA-directed alpha therapy with inhibitors of double-strand DNA break repair may potentiate efficacy at low toxicity. Furthermore, combination with inhibitors of the androgen receptor may enhance radiation delivery by increased PSMA expression on tumor cells (*23,24,25*).

In summary, alpha therapy is effective in patients with metastatic prostate cancer. Short range alpha emission targets small lesions more effectively than beta radiation. Given this advantage, cure of metastatic disease should be the ultimate goal of future alpha therapy research. In this intent, evaluation of early treatment and systemic PSMA-directed alpha therapy in conjunction with synergistic pharmacologic approaches are highly encouraged.

ACKNOWLEDGEMENT

We thank Dr. Norbert Müller for help with calculation of ^{225}Ac and ^{177}Lu radiation volumes.

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FIGURES

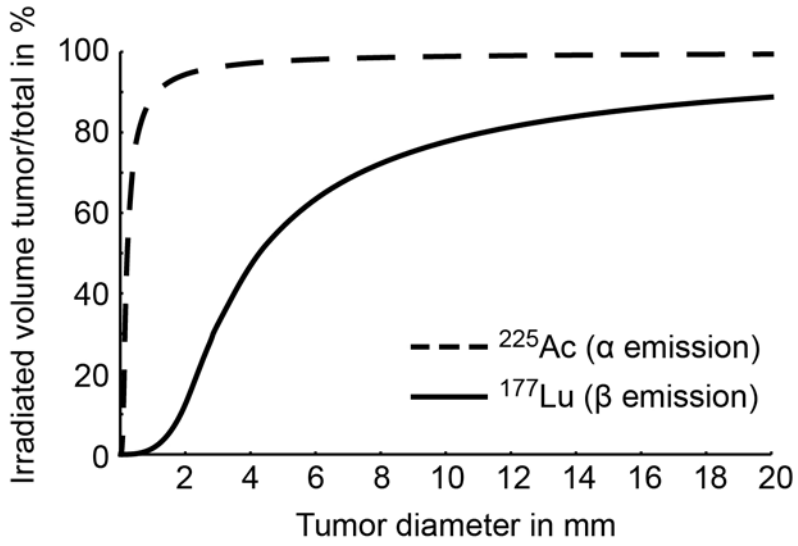

Figure 1: Proportion of targeted tumor volume per total irradiated volume for alpha (^{225}Ac) versus beta (^{177}Lu) radioligand therapy of small prostate cancer lesions. Maximum range in tissue was defined 0.1 mm for alpha and 2 mm for beta therapy. Radiation delivered to sub-centimeter lesions drops significantly for beta therapy, as energy deposition significantly extends beyond lesion boundaries. The simplified model calculates irradiated volumes based homogeneous intra-tumoral distribution of ^{225}Ac and ^{177}Lu without taking into account any potential difference in biodistribution, energy transfer and relative biologic effectiveness.