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Editorial

Should Low Molecular Weight PSMA Targeted Ligands Get Bigger and Use Albumin Ligands for PSMA Targeting?

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Abstract

Prostate Specific Membrane Antigen (PSMA) is strongly expressed in prostate cancer. Recently a number of low-molecular-weight inhibitors have demonstrated excellent PSMA targeting activity for both imaging as well as Lutecium-177 radiotherapy in human trials. The paper by Choy et al raises the question of whether we can further increase the effectiveness of PSMA targeted therapy by adding an albumin-binding entity to low-molecular-weight agents

The article by Choy and co-workers on the effectiveness of Lutecium-177 labeled phosphoramidate based PSMA inhibitors provides important insights into the evolving role of low molecular weight PSMA imaging and therapeutic agents for prostate cancer (1). When the first prostate cancer imaging agent, capromab pendetide, Prostascint, was developed, the target was unknown. Our lab used the antibody to clone the encoding DNA which we designated prostate specific membrane antigen, PSMA (2,3). It soon became apparent that PSMA and the brain peptidase protein NAALADase were the same protein (4). This was highly useful information because many effective inhibitors of NAALADase, such as urea linked glutamate, were already known (5). Most of the current low molecular weight imaging/therapeutic PSMA radionuclides contain urea linked glutamate. An excellent recent review of studies using low molecular weight PSMA targeted radiolabeled ligands is available (6). Compared to antibodies, the rapid tumor uptake and clearance of low molecular weight agents makes them more effective for imaging. Our lab demonstrated that the background clearance of urea-based PSMA ligands can be further accelerated by applying additional negative charges to the backbone (7). Indeed other modifications can be developed beyond the glutamate region with a linker like urea as there is a high tolerance for substitutions.

Choy et al increased tumor uptake by using phosphoramidate instead of urea to link to the glutamate. They introduced a side linkage which contains a ligand for reversible binding to albumin (1). This modification was based on the observation, by Mueller et al, that the addition of an albumin binding moiety increased tumor uptake of a ^{177}Lu Folate ligand by reducing the uptake and excretion by the kidneys (8). The Mueller article reported that their ^{177}Lu Folate-albumin linked analogue successfully controlled tumor growth in their animal model (8). As PSMA ligands are rapidly cleared following uptake and excretion through the kidney, Choy et al utilized the albumin binding strategy for their phosphoramidate-based ligand and likewise achieved vastly improved tumor control with their ^{177}Lu PSMA analogue (1). They observed both improved tumor to kidney ratios and continued increase in tumor uptake over time, with tumor to blood ratios of 300 to 1 (1). The leaky nature of tumor neovasculature allows albumin-bound larger molecules to preferentially

access tumors through the non-targeted-process of "enhanced permeability and retention effect and at the target site allows enhanced PSMA targeted tumor uptake and prolonged radioligand retention." These two studies suggest that the addition of an albumin binding moiety to targeting agents with rapid renal excretion results in higher tumor uptake and better tumor control with no significant increase in host toxicity (1,8). Both groups' results reflect consistent findings in two different animal models utilizing different tumor targeting ligands (1,8)

However, some factors need to be considered before we generalize the findings of Choy et al. Animal models often lack the heterogeneity seen in human studies and the site distribution seen in metastases, particularly bone metastatic disease of prostate cancer. Choy et al chose to use PC-3 cells, which are transfected to express PSMA, as a model. They observed excellent tumor control of most tumors, but some began to grow. Although the investigators did not examine the mechanisms of "resistance," some of the PC-3 cells may have evaded treatment because they had reduced or eliminated PSMA expression. While PC-3 cells are good models for demonstrating targeting, they have no AR and are not androgen responsive. Most human prostate cancers retain androgen receptors and androgen receptor driven activity even following androgen deprivation. The role of AR in radiation response needs to be taken into account. For instance, Some tumors contain a mutation, TMPRSS2-ERG, which is AR activated and reduces the effectiveness of ionizing radiation treatment by enhancing non-homologous end joining repair. This could not be assessed using PC-3 cells (9). It would be useful to test Choy's ligand on a broader range of human prostate cancers, especially those that have androgen receptor associated activity. Continuing improvements in the isolation of circulating tumor cells in identifying PSMA protein levels and changes in gene expression that occur following exposure to ionizing radiation may make it easier to ascertain the mechanism of resistance.

In terms of toxicity, Choy et al observed that mouse body weight was not significantly changed with prolonged retention of their Lutecium-177 agent in the blood (1). Still the impact of binding albumin on radionuclide accumulation in the kidney and lacrimal gland is worrisome and needs further evaluation. Human trials of both ^{177}Lu DOTAGA-(I-y)fk(SubKuE) PSMA and 177-Lu-PSMA-617 PSMA-have been encouraging, with a good tumor response and good tolerance of the patients to treatment in a heavily pretreated population (10,11). Even so, one has to wonder whether a modification like that with an albumin binding agent could achieve an even better response.

It has been nearly 30 years since the emergence of the first agent targeting prostate specific membrane antigen. During this period we have witnessed a shift from the enthusiasm for large molecular weight monoclonal antibodies, to the current preference for low molecular weight PSMA targeted inhibitors. This is a reflection of the general evolution of theranostic agents. Choy et al. used a small molecule reversibly bound to a larger protein, albumin, to achieve better tumor uptake and enhanced PSMA targeted anti-tumor activity. By offering an intriguing compromise between large and small, Choy and colleagues provide research results which merit further consideration and study (1).

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