

Mechanistic Insights for Optimizing PSMA Radioligand Therapy

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SUMMARY

PSMA radioligand therapy is a promising new class of therapy for prostate cancer. Heterogeneity of PSMA expression is an important factor explaining variability in clinical results. The ability to visualize the target with theranostics provides unique

mechanistic insights. Potential clinically applicable strategies to improve patient selection and optimize therapeutic efficacy are discussed.

See related article by Current et al., p. 2946

In this issue of *Clinical Cancer Research*, Current and colleagues provide mechanistic insights into a promising new class of therapy in advanced prostate cancer which targets prostate-specific membrane antigen (PSMA; ref. 1). They used mouse models to elegantly demonstrate a direct relationship between Lutetium-177 (¹⁷⁷Lu) PSMA radioligand uptake and consequent DNA damage. They demonstrate that both the percentage levels within tumor, reflecting spatial heterogeneity, as well as cell surface PSMA receptor expression density are important. Furthermore, they demonstrate effects are potentially magnified by using the alpha-emitter, Actinium-225 (²²⁵Ac), despite the spatial heterogeneity. The relationship between cell surface PSMA receptor expression and ²²⁵Ac PSMA therapy was not studied. As also acknowledged in the article, methodologic limitations included the use of a limited number of prostate cancer cell lines, some mouse derived, and an immune-deficient mouse model, which does not reflect the clinical reality.

Prostate cancer is the commonest cancer in men, and a leading cause of cancer-related death. The clinical spectrum of prostate cancer is broad, with unmet needs ranging from reducing overdiagnosis and overtreatment of early-stage, low-grade, disease to improving outcomes in patients with aggressive metastatic castrate-resistant prostate cancer (CRPC), which has high morbidity and mortality despite multiple recent therapeutic advances.

PSMA is highly overexpressed in CRPC, and the clinical experience of PSMA radioligand therapy (RLT) is largely in this patient population. Promising response rates with limited short-term toxicities have been demonstrated. Other available life-prolonging therapies in CRPC include taxane-based chemotherapies, newer generation anti-androgen therapies and the bone seeking radionuclide Radium-223. Recent clinical trials have also demonstrated markedly improved overall patient survival when most of these conventional therapies are used in the earlier castrate sensitive phase of the disease, leading to a paradigm shift in patient management. While the current clinical

challenge with PSMA RLT is to develop high-level evidence and establish a place in the management of CRPC, more benefit may ultimately occur by moving it earlier in the course of disease where there may potentially be greater clinical benefits.

The optimal selection of CRPC patients for PSMA RLT is not completely elucidated. Theranostics is the concept of patient selection for a targeted radionuclide therapy based on the imaging phenotype on a companion diagnostic scan. Typically, patients have progressed despite conventional therapies, and are selected based on PSMA overexpression (variably defined) as seen on a PSMA positron emission tomography (PET) scan. However, as Current and colleagues also point out, a significant proportion of patients do not respond to PSMA RLT despite using the theranostic approach. The explanation for the observed clinical heterogeneity likely lies in heterogeneous tumor biology with prior therapies leading to Darwinian selection of multiple clones of tumor, some of which may have low PSMA-expression or be radioresistant.

How may we use our currently available tools to optimize patient selection, predict treatment response, and improve the efficacy of PSMA RLT (Fig. 1)? There are baseline factors which portend a poor prognosis with conventional therapies, and also appear to equally apply to PSMA RLT (2). These include requirement for opioid analgesia, poor ECOG status, high LDH, high volume bone metastases (reflected by high ALP or high bone scan index), and visceral metastases.

In our practice, we have also found it useful to classify patients according to the imaging phenotype demonstrated on screening using both fluoro-deoxy-glucose (FDG) and PSMA PET scans. We attribute our relatively high PSA \geq 50% response rate in our prospective trial using ¹⁷⁷Lu PSMA RLT of 64% to this use of PET to optimize patient selection (3). Remarkable, only two of 50 patients in our study had no reduction in PSA.

One of the advantages of molecular imaging is the striking ability to visualize tumor heterogeneity. Some patients with highly PSMA-avid disease also have metastases that have lost PSMA-expression. Around 11% (8/75) of patients screened for our study were ineligible due to this phenomenon, identified by the presence of metastases with high FDG-avidity but low or no PSMA expression. FDG-avidity was also useful among patients who proceeded to PSMA RLT, as the baseline metabolic tumor volume was highly prognostic (4). These results demonstrate both the prognostic impact of both tumor heterogeneity and glucose hypermetabolism, when using this targeted therapy in a heavily pretreated patient cohort. This is unlikely to be overcome by PSMA RLT using ²²⁵Ac alpha particles, which in this situation has the disadvantage of a shorter path-length in tissue leading to less “cross-

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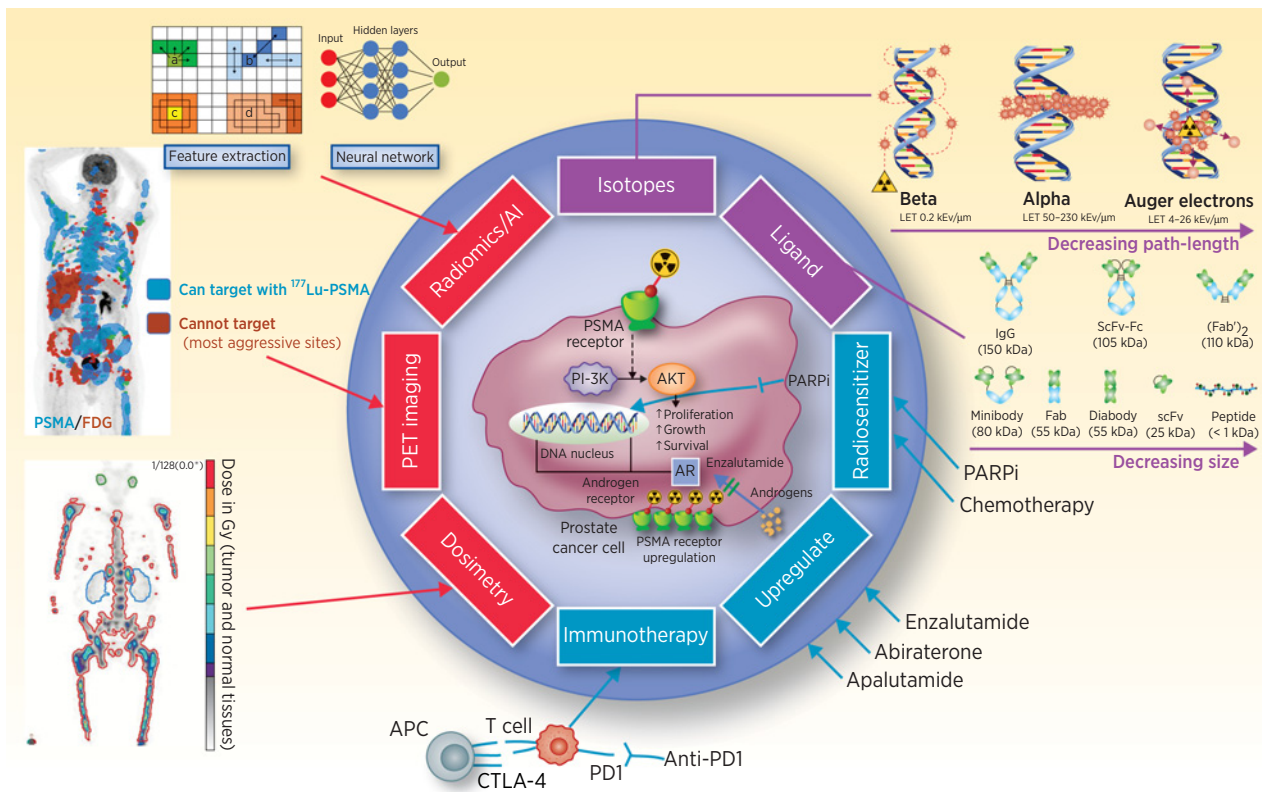


Figure 1. Potential mechanisms to optimize PSMA Theranostics. Center, prostate cancer cells with PSMA-receptor. Red, using nuclear medicine techniques including radiomics, PET imaging to identify tumor heterogeneity and dosimetry to measure radiation dose delivered to tumor and normal tissue. Blue, potential combination therapeutic combination including immunotherapy, drugs to upregulate PSMA expression or drugs to enhance effects of radiation damage (radiosensitizers). Purple, use of different radioactive isotopes (beta-, alpha-, or Auger-electrons) or newer generation targeting ligands. AI, artificial intelligence.

fire” radiation and less damage to nearby tumor cells, which may have lower PSMA expression. In this context, a beta emitter such as Yttrium-90 (⁹⁰Y) with longer path length in tissue (and thus higher “cross-fire” radiation) may be a consideration. Treatment approaches which do not purely target PSMA are also required in this situation.

Current and colleagues results that lower PSMA expression results in lower radiation absorbed doses and lower DNA damage are also reflected in our clinical experience. A subset of our treated patient cohort underwent dosimetry, and we demonstrated that only one of 11 patients with a whole body tumor absorbed dose under 10 Gy had a PSA response ≥ 50% (4). During screening for our study, a further 11% (8/75) patients were also excluded on the basis of low PSMA expression at all sites, defined as less than 1.5 times hepatic background uptake. Further research is needed as the apparent PSMA uptake on a PET scan also depends on technical factors including lesion size, motion artefact, reconstruction parameters etc, and the absolute lower limit for treatment futility is not known. There may also be compelling clinical reasons to proceed with PSMA RLT on a compassionate basis to improve quality of life in some symptomatic patients who may have no other treatment options.

Although RLT may represent a new life-prolonging therapy for men with CRPC, all patients eventually progress and responses may not be durable. Accordingly, there is an urgent need to further optimize RLT. One approach, is using alpha particles as an attempt to maximize local radiation dose deposition but this comes at the cost of more severe

xerostomia due to salivary irradiation. Notably, Current and colleagues did not study the preclinical effect of Ac-225 PSMA in tumors with different cellular levels of PSMA expression so effects of alpha-versus beta-radiation in low PSMA expression warrants further investigation. Combining alpha- and beta-radiation is another therapeutic option.

Chemotherapy, immunotherapy, and PARP inhibitors may all be potential combinations to enhance the effectiveness of single agent PSMA RLT, but need to be studied for dose finding, tolerability and efficacy. If successful, these approaches may potentially be translated to patients with the more heterogenous imaging phenotype of FDG avid discordant disease.

Other future approaches to optimize PSMA RLT may include better patient selection with liquid biopsies or sophisticated image analysis using radiomics and machine learning to elucidate disease heterogeneity, molecular or genetic markers for radiation sensitivity, prospective dosimetry to avoid futile therapy, increase radiation dose delivery firstly by optimizing the currently used empiric administered activities and schedules (5), and studying more sophisticated approaches, for example, pharmacologic manipulation to upregulate PSMA expression, development of bivalent or higher affinity peptides.

Most importantly, and in a crowded clinical landscape, there is a requirement for well-designed prospective clinical trials to show superior or comparable efficacy (and safety profile) to established conventional life-prolonging therapies. This should also focus on

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moving PSMA RLT to an earlier stage in the management of prostate cancer where the clinical benefits may be highest.

Disclosure of Potential Conflicts of Interest

M.S. Hofman reports receiving other commercial research support from AAA/Novartis and speakers bureau honoraria from Janssen. No potential conflicts of interest were disclosed by the other author.

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