

Invited perspective:

Why Targeting PSMA is a valuable addition in the management of castration-resistant prostate cancer: The Urologists' point of view

Boris A. Hadaschik, MD¹, Martin Boegemann, MD²

¹Department of Urology, University Hospital Essen, Essen, Germany

²Department of Urology, University Hospital Münster, Münster, Germany

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For correspondence:

Prof. Dr. Boris Hadaschik

Department of Urology

University Hospital Essen

Hufelandstr. 55

45147 Essen

Germany

E-mail: boris.hadaschik@uk-essen.de

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Abbreviations:

AA: abiraterone acetate

ADT: androgen deprivation therapy

AR: androgen receptor

CRPC: castration resistant prostate cancer

ENZA: enzalutamide

PC: prostate cancer

PSA: prostate-specific antigen

PSMA: prostate-specific membrane antigen

PET: positron emitting tomography

rPFS: radiographic progression-free survival

Prostate cancer (PC) is the most common cancer and the third most common cause of cancer-related deaths in men in developed countries (1). In general, PC starts out as an androgen-dependent tumor. Thus, androgen-deprivation therapy (ADT) represents the backbone of treatment for metastatic PC (2). However, disease progression usually occurs within a few years despite of castrate levels of serum testosterone, defining a state called castration resistant prostate cancer (CRPC). The majority of these patients develop resistance to castration due to a reactivation of the androgen receptor (AR) signaling axis. In the last decade, several drugs have been shown to provide a survival benefit for men with metastatic CRPC. However, prediction of response is challenging and the optimal choice out of several treatment options has to be made on an individual basis. Currently, the most frequently used 1st line treatment for asymptomatic or minimally symptomatic metastatic CRPC are abiraterone acetate (AA) plus prednisone, enzalutamide (ENZA) or sipuleucel-T (in North America). AA is an inhibitor of CYP17 which is a key enzyme required in testosterone synthesis. Enzalutamide is a 2nd generation antiandrogen which inhibits androgen binding to the androgen receptor, inhibits androgen receptors from entering the cell nucleus and inhibits the androgen receptor from binding to DNA and from serving as a transcription factor. Sipuleucel-T is a personalized, autologous, cellular vaccine against prostatic acid phosphatase combined with GM-CSF. In 2nd line or in symptomatic CRPC therapy consists of taxane chemotherapy (docetaxel or cabazitaxel), radium-223 or AA/ENZA (whichever has not been used in 1st line). Taxanes disrupt the orderly microtubule function while Radium-223 is a calcimimetic which decays while emitting alpha radiation and internally radiates bone metastases. In contrast to AR-targeting strategies, 'unspecific' cytostatic chemotherapies can be effective in mCRPC, even when 1st and 2nd line hormonal therapies fail. However, these are associated with considerably more side effects. In patients, not willing to be treated with chemotherapy and/or not eligible for chemotherapy, due to the respective toxicity profile, AA or ENZA are often used as 2nd line therapy of choice. However, the 2nd line treatment success of AA or ENZA is often times limited and short lived due to cross-resistance caused for example by

alternative splicing of the AR (3,4). Novel targeted therapies with favorable toxicity profiles are therefore needed to broaden the therapeutic armamentarium.

Amongst others, the prostate specific membrane antigen (PSMA), a transmembrane protein, which is physiologically expressed in prostate cell membranes but highly overexpressed in primary prostate cancer and increasingly more in CRPC metastases, seems to be a very promising molecular target both for imaging of tumor spread and for radioligand therapy (5,6). Over the past years, PSMA-targeting positron-emitting-tomography (PET) tracers such as ^{68}Ga -PSMA-11 significantly improved diagnostic pathways in prostate cancer (7). PSMA-PET/CT or -MRI should be considered the new gold-standard for imaging of men with biochemical recurrence. General challenges for PSMA-imaging are few tumors without PSMA-expression. Ligand specific challenges for ^{68}Ga -PSMA-11 PET/CT are evaluation of bladder infiltration due to the excretion of PSMA-11 via the urinary tract, the availability of the radionuclide, which is limited by generator-capacity, and the short half-life of ^{68}Ga (68 min) which prohibits delivery to distant PET centers. Therefore, ^{18}F -labeled PSMA-tracers are under investigation that could be produced in large amounts in a cyclotron and whose longer half-life (110 min) would enable transfer to satellite institutions (8,9).

Besides imaging, PSMA-targeted endoradiotherapy of metastatic CRPC is emerging. Several recent retrospective studies have shown a high potential of the PSMA-targeted radioligand ^{177}Lu -PSMA-617 applied under a compassionate use provision in end stage metastatic CRPC patients (10-16). Upon ligand binding PSMA and its bound molecule are internalized via clathrin-coated pits and subsequent endocytosis. Since internalization leads to enhanced uptake of activity and retention, targeting PSMA results in a high local intracellular deposit for therapeutic applications. While the β -ray emitting component of ^{177}Lu -PSMA-617 efficiently irradiates these cells, the γ -component can be used for imaging. As demonstrated by promising PSA-declines, this innovative therapy is effective in patients with end stage metastasized PC while exhibiting a favorable toxicity profile (10-16). A recent study on ^{177}Lu -PSMA-617 radioligand therapy with up

to now the largest cohort of patients (n=145) has shown a considerable response rate with a PSA decline $\geq 50\%$ in 45% of patients (12). Alkaline phosphatase < 220 U/l, the absence of visceral metastases and the number of therapy cycles were relevant independent predictors of biochemical response. Interestingly, prior chemotherapy did not significantly influence response rates.

Currently, radioligand therapy using PSMA-ligands is limited to the treatment of metastatic CRPC patients with progressive disease despite prior treatment with at least two lines of approved and endorsed strategies per multidisciplinary guidelines and/or objective exclusion criteria against the use of as of yet not given remaining options. However, because of the excellent toxicity profile it is a clear intention of prostate cancer patients and patient organizations that this new and promising therapy option should be made available already in earlier stages of the disease; in these stages patients might have a superior benefit, longer progression free survival and improved quality of life as they exhibit a better performance status and lower tumor burden. Based on the hitherto existing observations and experiences, prospective multicenter studies with more homogeneous groups of metastatic CRPC patients are currently being planned in Germany.

From the urologists' point of view, these future studies must not focus on PSA-declines alone, but on radiographic progression-free survival (rPFS) as intermediate primary endpoint. Since the introduction of PSA in the context of screening, PC diagnosis and management have been guided by this easily measurable serum biomarker. PSA levels have been shown to be associated with disease burden and are included in many prognostic tools for survival. However, in some patients the PSA test may lead to investigations which can identify clinically insignificant cancers which would not have become evident in a man's lifetime and cause over-treatment. Therefore, the role of PSA as a screening test is being discussed controversially (17).

In metastatic patients, assessment of PSA levels over time is routinely used to evaluate

treatment response. While PSA is very helpful in men with castration-sensitive disease, the correlation between PSA-levels and survival becomes more complex in advanced disease states which are characterized by increasing disease heterogeneity due to the complex mechanisms surrounding development of castration-resistance (18,19). Assessment of therapy response by PSA alone can be impaired by flare phenomena (20) and by the presence of visceral metastases not producing PSA (21). Consequently, conventional imaging methods, including computed tomography, magnetic resonance imaging and bone scintigraphy have been proposed as tools to evaluate the response to therapy by the Prostate Cancer Clinical Trials Working Group 3 (22). The association between rPFS and overall survival is still being investigated, but a consistent and high association has been demonstrated recently (23). Standardized imaging is key for patient management, biomarker development and therapeutic clinical trials.

Approximately one third of patients treated in experienced ^{177}Lu -PSMA-617 centers did not respond despite PSMA-overexpression in prior PET-scans. In order to break this primary radio-resistance to the β -emitter Lutetium and to further reduce hematological toxicity, targeted α -radiation might be a possible solution. Consequently, first-in-human results of ^{225}Ac -PSMA-617 presented by Kratochwil et al. from Heidelberg are an important step forward (24). The two patients presented were heavily pretreated men with end-stage metastatic CRPC. Strikingly, both subjects achieved a complete response on PSMA-PET imaging and PSA-declines below measurable levels. As expected from a cell-specific radiotherapy with very short range, hematologic toxicity was low, but both men suffered from enduring xerostomia subsequently. More recently, 14 patients were reported demonstrating an impressive anti-tumor activity by means of objective radiological response or tumor marker decline in 9/11 evaluable patients (25). A treatment activity of 100 kBq/kg ^{225}Ac -PSMA-617 per cycle repeated every 8 weeks was suggested as a reasonable trade-off between toxicity and anti-tumor activity. Certainly, these

excellent results will have to be validated in larger cohorts and at different centers.

In conclusion, PSMA-targeted radioligand therapy is a very promising and exciting addition to the therapeutic spectrum in men with metastatic CRPC. However, prospective clinical trials with appropriate clinically relevant endpoints are not available yet. Moreover, the optimal timing of their use, predictive and prognostic biomarkers, possible combinations with other systemic drugs and best treatment sequences are unknown as of yet. These challenges will best be solved using a multidisciplinary approach and treatment in the context of clinical trials.

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