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THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

^{18}F -NaF/ $^{223}\text{RaCl}_2$ theranostics in metastatic prostate cancer: treatment response assessment and prediction of outcome

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ABSTRACT

Theranostics refers to companion agents with identical or similar structure targeted to a specific biological entity for imaging and treatment. Although the concept has a long history with radioiodine in thyroidology, but it has experienced remarkable recent renaissance in management of neuroendocrine tumors and prostate cancer. Bone scintigraphy based on osteoblastic reaction and targeted radionuclide therapy with the alpha-particle calcium-mimetic agent, $^{223}\text{RaCl}_2$, also form a theranostic model for imaging and treatment of osseous metastatic disease. Since the regulatory approval of $^{223}\text{RaCl}_2$ in 2013, there has been accumulating evidence on the potential use of ^{18}F -NaF PET scintigraphy in the assessment of response and prediction of outcome in males with metastatic castrate-resistant prostate cancer who undergo $^{223}\text{RaCl}_2$ therapy. We review the ^{18}F -NaF/ $^{223}\text{RaCl}_2$ as theranostic companion in the management of prostate cancer with emphasis on the utility of ^{18}F -NaF and other relevant PET radiotracers in the therapy response and prognosis assessments.

Theranostics had its beginning in diagnosis and treatment of thyroid diseases with radioiodine more than 75 years ago, although this specific designation was probably coined more recently.¹ Theranostics is a systematic integration of targeted diagnostics and therapeutics as companion agents that facilitates precision medicine by identifying subset of patients who would benefit from a particular treatment based on imaging evidence for expression of the intended biological target. This fast-growing field, with more recent strides in care of patients with prostate cancer and neuroendocrine tumors, has been recognized as one of the priorities in future cancer research.²

There are now several approved treatments available for metastatic castrate-resistant prostate cancer (CRPC). These include drugs that target the androgen axis, such as abiraterone acetate (androgen synthesis inhibitor) and enzalutamide (androgen receptor antagonist), cabazitaxel (novel taxane chemotherapy), sipuleucel-T immunotherapy (cancer vaccine), and alpha particle therapy of bone lesions with $^{223}\text{RaCl}_2$.^{3–5} The most optimal patient selection or drug sequencing criteria is not yet established and will need further understanding of the biological drivers of resistance

to various treatments, cross-reactivity of treatments, and effect of tumor heterogeneity.^{6,7} However, type of prior treatments, tumor burden, symptoms, performance status, comorbidities, and patient and physician preferences may also be other factors to consider.

Alpha particle therapy with $^{223}\text{RaCl}_2$ targeted to osteoblastic metastatic bone lesions is the first-in-class of such treatments that has been shown to be safe and effective and was approved by the Food and Drug Administration (FDA) on May 15, 2013.^{8–15} $^{223}\text{RaCl}_2$ is included in the US, UK and European guidelines and the nuts and bolts and practical considerations for clinical practice and patient management have been published.^{16–19}

A recent study has demonstrated that $^{223}\text{RaCl}_2$ can be safely combined with other treatments that are associated with improved outcome when compared to $^{223}\text{RaCl}_2$ alone.²⁰ Overall survival was also found to be longer in those patients who had normal range baseline alkaline phosphatase level, hemoglobin level 10 g dl⁻¹ or greater, Eastern Cooperative Oncology Group Performance status of 0, and no pain in comparison to those patients who did not satisfy these parameters. This study

suggested that $^{223}\text{RaCl}_2$ might be used in asymptomatic patients (in contradistinction to the inclusion criterion of the ALSYMPCA trial) and with other treatments for improved outcome. In another retrospective investigation of 64 males with metastatic CRPC, a multivariate analysis showed that no prior chemotherapy, oligometastatic disease (≤ 5 bone metastases), baseline alkaline phosphatase $<115 \text{ U l}^{-1}$, and alkaline phosphatase response after $^{223}\text{RaCl}_2$ therapy were predictive stratification factors of improved survival.²¹ In a recent investigation, a multivariable analysis showed that previous sipuleucel-T treatment ($p = 0.009$), hemoglobin $\geq$ lower limit of normal (LLN) ($p = 0.037$), and absolute neutrophil count (ANC) $\geq$ LLN ($p = 0.029$) were significantly associated with the probability of completing the entire 6-cycle course of $^{223}\text{RaCl}_2$ treatment.²² Treatment with $^{223}\text{RaCl}_2$ may also benefit patients with hormone-sensitive bone metastases after radical prostatectomy. Overall, $^{223}\text{RaCl}_2$ tends not to lead to sustained PSA decline but decrease in alkaline phosphatase is often observed. This is because PSA is also reflective of soft tissue disease while bone alkaline phosphatase is a more

relevant parameter related to proliferating osteoblasts reacting to tumor cells.²³

TREATMENT RESPONSE ASSESSMENT

Documentation of response to $^{223}\text{RaCl}_2$ therapy with imaging is not well established and needs evaluation in the setting of available PET radiotracers and optimal timing for assessment after therapy.^{24,25} ^{18}F -NaF PET, like $^{99\text{m}}\text{Tc}$ -based bone scintigraphy, may show treatment flare in responding lesions. In one case report in a patient receiving $^{223}\text{RaCl}_2$ therapy for metastatic CRPC, both bone pain and PSA level increased initially but during follow-up bone scan showed evidence of response with marked decline in bone pain and PSA level²⁶ (Figure 1). Keizman and colleagues suggest that radiological flare may be noted during the first 3 months of treatment and should not be considered as progression. Potential extraskeletal progression may be assessed with CT in case of PSA rise or other suspicious signs and symptoms.²⁷ Kairemo and Joensuu evaluated retrospectively the use

Figure 1. Radionuclide bone scan trend and response to $^{223}\text{RaCl}_2$ therapy. (a) June 2008, metastatic prostate cancer diagnosis. (b) May 2010, disease progression on combined androgen blockade. (c) May 2011, disease progression following sipuleucel-T immunotherapy. (d) December 2011, disease progression just prior to docetaxel chemotherapy. (e) June 2013, widespread disease progression associated with severe diffuse bone pain on enzalutamide ("pre- $^{223}\text{RaCl}_2$ "). (f) February 2014, dramatic theranostic clinical and bone scan response 20 months after completing six treatments of $^{223}\text{RaCl}_2$ ("post- $^{223}\text{RaCl}_2$ "). From McNamara et al.²⁶ Courtesy of BioMed Central under the Creative Commons Attribution.²⁶

of ^{18}F -NaF PET/CT in assessment of response after the first and sixth cycles of $^{223}\text{RaCl}_2$ in 10 patients with metastatic CRPC.²⁸ A modified version of PERCIST (PET Response Criteria in Solid Tumors) criteria was used. A reduction (range 6.9–68.4%) of ^{18}F -NaF localization in bone lesions was noted after all 6 cycles of $^{223}\text{RaCl}_2$ in accordance with decline in PSA level. Such decline was not seen after 1 cycle of therapy and in fact in 2 patients, flare might have been present.

The repeatability of ^{18}F -NaF quantitation is important, if it is destined to be a useful imaging tool in the assessment of response to therapy. In a multi-center investigation of 35 males with metastatic CRPC, test-retest ^{18}F -NaF PET/CT scan were performed within 3 ± 2 days apart.²⁹ Using sufficiently large bone lesions ($>1.5\text{ cm}^3$), the authors showed that at the lesion level, the coefficient of variation for maximum standardized uptake value (SUVmax) and SUVmean were 14.1 and 6.6%, respectively. At the patient level, the coefficient of variation for SUVmax and SUVmean were 12.0 and 5.3%, respectively. Despite these differences, the authors felt that ^{18}F -NaF PET/CT repeatability level at a particular imaging site might be sufficient for clinical quantification of response of bone metastases to therapy. Another study showed that there could also be differences in relation to type of the PET imaging system, particularly with respect to use of time-of-flight (TOF) measurements.³⁰ Osseous metastatic lesions showed higher SUVmean values (by about 2.5%), while normal soft tissues showed lower SUVmean with TOF. These studies suggest that it is most optimal to use the same type of imaging systems in follow-up of patients before and after therapy to reduce the effects of variability in lesion quantitative measures.

Murray et al investigated whether the bone lesion absorbed dose after administration of $^{223}\text{RaCl}_2$ correlated with level of ^{18}F -NaF uptake in 5 patients with metastatic CRPC.³¹ There was a high correlation ($r = 0.96$) between $^{223}\text{RaCl}_2$ absorbed dose and ^{18}F -NaF uptake suggesting that those metastatic lesions with higher ^{18}F -NaF uptake will also receive higher $^{223}\text{RaCl}_2$ dose, in alignment with the general concept of theranostics with these paired agents.

Cook and colleagues performed ^{18}F -NaF PET/CT in 5 patients with CRPC and only bone metastases before, at 6 weeks and at 12 weeks after $^{223}\text{RaCl}_2$ therapy (100 KBq kg^{-1} at 0 and 6 weeks).³² The mean SUVmax of 5 selected bone metastases decreased at 12 weeks in correspondence to PSA decline in 3 patients and decline in alkaline phosphatase in 4 patients. This study suggested that ^{18}F -NaF PET/CT may be useful in assessing response to $^{223}\text{RaCl}_2$ therapy. Similar utility of ^{18}F -NaF PET/CT in assessing response has been reported with chemotherapy and androgen receptor pathway inhibitors which can also be predictive of progression-free survival.³³ In an imaging companion trial [American College of Radiology Imaging Network (ACRIN) 6687] to a multicenter metastatic CRPC tissue biomarker-guided therapeutic trial (NCT00918385), Yu et al showed statistically significant decline in SUVmaxavg (average of SUVmax of up to 5 lesions) in response to dasatinib, which also correlated with changes in bone alkaline phosphatase but not PSA levels.³⁴

The extent of bone disease on bone scintigraphy, including ^{18}F -NaF PET/CT, may have significant implications on experience of hematotoxicity and the number of $^{223}\text{RaCl}_2$ cycles that may be tolerated with higher bone tumor load (*i.e.* less bone marrow reserve) associated with higher rate of Grade 3 or above toxicity and early therapy termination.³⁵ Finally, a large cohort national study (National Oncologic PET Registry, NOPR) has shown that ^{18}F -NaF PET is not only useful in treatment response assessment but also can impact management in up to 40% of patients.³⁶ More recent NOPR data analysis revealed not only concordance between intended post- ^{18}F -NaF PET management plans and inferred management based on inquiry of Medicare claims but also an association between ^{18}F -NaF PET results and subsequent hospice claims and patient survival.^{37,38}

PROGNOSIS AND PREDICTION OF OUTCOME

The baseline burden of metastatic disease has been demonstrated to be predictive of outcome. Jadvar et al showed in a prospective study of 87 patients with metastatic CRPC undergoing FDG PET/CT that the continuous parameter sum of SUVmax of up to 25 metastatic lesions (both bone and soft tissue) was significantly ($p = 0.053$) predictive of overall survival with a hazard ratio of 1.01 [95% confidence interval (CI), 1.001–1.02]. When sum of SUVmax was grouped into quartile ranges, there was poorer survival probability for the patients in the fourth-quartile range than for those in the first-quartile range, with a univariate hazard ratio of 3.8 [95% CI (1.8–7.9)].³⁹ A recent investigation focusing only on bone metastases arrived at a similar conclusion that baseline skeletal tumor burden as demonstrated on ^{18}F -NaF PET scintigraphy is a prognostic biomarker of overall survival and hematological toxicity in patients receiving $^{223}\text{RaCl}_2$ therapy.⁴⁰

Zukotynski and colleagues evaluated the prognostic utility of ^{18}F -NaF and FDG in 9 patients with metastatic CRPC in a Phase 1 trial of abiraterone and cabozantinib therapy.⁴¹ The Kaplan-Meier survival analysis showed a statistically significant difference in progression free survival (PFS) among males with widespread FDG-avid, oligometastatic FDG-avid, and non-FDG-avid disease. Extent of osseous disease on ^{18}F -NaF PET/CT was not predictive of treatment response. The authors concluded that FDG might be superior to ^{18}F -NaF in the imaging evaluation of response to treatment with abiraterone and cabozantinib. However, in another relatively similar study evaluating zibotentan therapy, the authors suggested that FDG and ^{18}F -NaF uptake levels in lesions may be spatially dislocated and both tracers provide useful complementary information.⁴²

Apolo et al reported on a prospective pilot study of ^{18}F -NaF PET/CT in predicting survival in patients with prostate cancer.⁴³ The patient cohort included 30 males with and 30 males without bone metastases on $^{99\text{mTc}}$ -based bone scintigraphy. ^{18}F -NaF PET/CT was performed at baseline, 6-month and 12-month, and the findings were correlated with PSA and overall survival. ^{18}F -NaF PET/CT detected more bone lesions than $^{99\text{mTc}}$ -based bone scintigraphy. The number of lesions on PET (extent of disease) correlated significantly with outcome. In fact, measurement of burden of active osseous metastatic disease on ^{18}F -NaF PET/CT is feasible and has been shown to be predictive

Figure 2. Contrasting patients with sequential ^{18}F -NaF PET/CT before and after treatment with $^{223}\text{RaCl}_2$. (a) Patient #1's baseline ^{18}F -NaF PET/CT demonstrates widespread osteoblastic metastases with high ^{18}F -NaF uptake. (b) After treatment with $^{223}\text{RaCl}_2$, patient #1 had significant signs of progression, with additional sites of osteoblastic metastases. Patient #2 (c) also had his baseline ^{18}F -fluoride PET/CT demonstrating widespread osteoblastic metastases with high uptake. Fortunately, patient #2 responded to treatment with $^{223}\text{RaCl}_2$ with marked skeletal tumor burden reduction (d). From: Rohren et al.⁴⁴ © by the Society of Nuclear Medicine and Molecular Imaging, Inc.⁴⁴

of overall survival and risk of skeletal related events in patients treated with $^{223}\text{RaCl}_2$ ^{44,45} (Figure 2). In order to determine suitable semi-quantitative parameters for skeletal tumor burden, an SUV_{max} threshold of 10 was used to calculate the fluoride tumor volume within a whole-body volume of interest (FTV_{10}) which excluded non-metastatic high activity sites such as renal collecting system, degenerative disease, and healing fractures. The total lesion fluoride uptake was calculated as a product of mean SUV_{max} and volume of interest (TLF_{10}). The parameter TLF_{10} was not only reproducible but at a cutoff level of 8000 was able to discriminate survivors from non-survivors after $^{223}\text{RaCl}_2$ therapy.⁴⁵

We assessed our one-year experience with $^{223}\text{RaCl}_2$ after its approval for use.⁴⁶ We observed that about one-quarter of our patient cohort of 25 were able to complete the entire six-dose treatment. Advancing soft tissue disease was the primary reason for cessation of therapy in the rest of the group. The adverse events were mild and manageable. We also noted that in responding patients, there was a decline in serum alkaline phosphatase,

which was more common than a decline in PSA level. The investigators from MD Anderson Cancer Center reported retrospectively on a similar experience with 110 patients who underwent $^{223}\text{RaCl}_2$ therapy.⁴⁷ They noticed treatment-related significant reduction in alkaline phosphatase and pain score. On multivariate analysis, the total number of $^{223}\text{RaCl}_2$ cycles and concomitant use of abiraterone were significantly associated with overall, progression-free, and bone event-free survivals.

COMPARATIVE UTILITY OF ^{18}F -NAF TO OTHER PET RADIOTRACERS

Bone imaging with ^{18}F -NaF is inherently indirect for identification of disease sites that have altered the bone microenvironment. It is of interest to decipher how bone imaging relates to direct imaging of marrow disease (particularly early involvement without major bony reactive changes) with the current and forthcoming PET agents. Beheshti and colleagues compared ^{18}F -NaF PET/CT and ^{18}F -fluorocholine (FCH) in patients with prostate cancer.⁴⁸ They concluded that although ^{18}F -NaF PET/CT is highly sensitive for detection of bone metastases but FCH PET/

CT provides greater specificity and can also detect early marrow involvement before there is significant osteoblastic reaction. FCH PET/CT may also be helpful in treatment response assessment and provide prognostic information (e.g. PSA progression) by monitoring changes in whole-body choline-avid tumor burden. In a cohort of 42 CRPC patients who underwent FCH PET/CT at baseline and 3 months after start of treatment (chemotherapy in 16, antiandrogens in 19, $^{223}\text{RaCl}_2$ in 5, and sipuleucel-T in 2), a significant decline ($\geq 30\%$) in net metabolically active tumor volume (MATV) (i.e. MATV response) was significantly associated with longer time to PSA progression in comparison to those patients who did not display a MATV response (481 vs 116 d, $p = 0.0067$), regardless of treatment type.⁴⁹ Miyazaki et al reported similar results noting significant decline in MATV and total lesion activity (TLA) on FCH PET/CT in patients responding favorably to $^{223}\text{RaCl}_2$ treatment.⁵⁰ In one comparative study of $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy, ^{18}F -NaF PET/CT and FCH PET/CT in 50 males with spinal metastases, the diagnostic performance of PET/CT studies were significantly higher than $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy prompting the investigators to question the value of $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy when PET/CT (with either ^{18}F -NaF or FCH) is available.⁵¹ The sensitivity and specificity were 51 and 82% for $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy, 93 and 54% for ^{18}F -NaF PET/CT, and 85 and 91% for FCH PET/CT with MRI used as standard of reference with characterizing bone lesions as likely malignant or benign. ^{18}F -NaF PET/CT provides high sensitivity with FCH PET/CT improving the specificity and both have been suggested to be included in the relevant guidelines as alternative to $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy in this clinical setting.^{52,53}

Imaging with radiolabeled agents targeted to the prostate specific membrane antigen (PSMA) in conjunction with PET/CT has received much attention over the past few years and is anticipated to exert a major transformational change in management of prostate cancer.⁵⁴ A recent prospective multi-center

Australian investigation involving 431 patients with prostate cancer (primary staging of intermediate-high risk disease in 25% and restaging/biochemical recurrence in 75% of patients) reported an overall change in planned management of about half of the patients with ^{68}Ga -PSMA-11 PET/CT.⁵⁵ PSMA PET/CT may also be useful to more accurately assess the extent of disease prior to a planned treatment with $^{223}\text{RaCl}_2$ based on bone scintigraphy. For example, the investigators from Münster, Germany, showed in a small cohort that 3 of their 4 patients with previously unknown visceral metastases (hence initially thought to be candidates for $^{223}\text{RaCl}_2$ therapy) were in fact not suitable for such treatment and that ^{68}Ga -PSMA PET/CT can be useful as gatekeeper in patient management in this clinical setting.^{56,57} Ahmadzadehfar and colleagues also demonstrated that ^{68}Ga -PSMA-11 can be a useful gatekeeper for $^{223}\text{RaCl}_2$ treatment in order to select patients who might benefit most from such therapy⁵⁸ (Figure 3). They also showed that PSA increase during therapy cycles is related to disease progression. The same group of investigators reported in a single case report that ^{68}Ga -PSMA-11 can be useful in documenting the tumoricidal effect of $^{223}\text{RaCl}_2$ therapy.⁵⁹ Radiolabeled PSMA PET may also be advantageous and more sensitive over ^{18}F -NaF for differentiation of treatment-induced “flare” from frank progressive disease as has been shown in single case reports.^{60,61}

CONCLUSIONS

Precision medicine is entirely aligned with theranostics, which is now emerging as an important systematic tool for targeted “see & treat” management of patients with cancer. Imaging with ^{18}F -NaF PET/CT and radionuclide therapy with $^{223}\text{RaCl}_2$ target osteoblastic metastatic bone lesions. Although the most optimal imaging method for assessing response to $^{223}\text{RaCl}_2$ therapy is not well established, ^{18}F -NaF PET can be useful if it is performed sufficiently after the end of treatment (about 2–3 months) to reduce the probability of treatment flare that can simulate progression. Pre-treatment total fluoride avid bone metastases

Figure 3. A 69-year-old patient with hormone-refractory prostate cancer (Gleason score, 8) who underwent bone scintigraphy (a) was referred for $^{223}\text{RaCl}_2$ therapy. ^{68}Ga -PSMA PET/CT (b) showed multifocal bone metastases concordant to bone scintigraphy. PSA level at time of PET imaging was 30 ng ml^{-1} , and ALP was 207 U l^{-1} . Patient underwent 6 cycles of therapy with $^{223}\text{RaCl}_2$ therapy and 4 weeks later showed near-complete response by ^{68}Ga -PSMA PET (c) and partial response by bone scintigraphy (d). PSA and ALP decreased to 2.95 ng ml^{-1} and 98 U l^{-1} , respectively. From: Ahmadzadehfar et al.⁵⁸ © by the Society of Nuclear Medicine and Molecular Imaging, Inc.⁵⁸

correlate with patient outcome. The utility of ^{18}F -NaF in comparison to other relevant PET radiotracers in the clinical setting of prostate cancer, particularly radiolabeled PSMA ligands, needs further exploration.

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