Reply: PSMA-Targeted Therapeutics: A Tale About Law and Economics

REPLY: I thank Dr. Notni for his recent letter in which he provides his perspective on one part of the success story of PSMA-targeted theranostics. Success stories often come with conflicts and intellectual ownership discussions.

Dr. Notni makes important points. He acknowledges the pivotal role of the inventors of $^{177}$Lu-PSMA I&T in shaping the field (1). He also emphasizes our obvious responsibility to honor patent protection. I would like to highlight that both patented and unpatented compounds can be successful and become market drivers. It is important to allow free market forces to compete for business. For instance, one company is currently initiating a phase 3 clinical trial with the nonpatented compound $^{177}$Lu-PSMA I&T in patients with castration-resistant prostate cancer (2). As another example, the U.S. Food and Drug Administration recently granted a new-drug application for the non–patent-protected $^{68}$Ga-PSMA-11 for a wide range of indications in patients with prostate cancer (3). This development further establishes the high clinical relevance and impact of PSMA-targeted PET imaging in the care of prostate cancer patients (4). Reimbursement will set the stage and prepare the market for several soon-to-be-approved compounds with comparable diagnostic performance. Then the market will decide which ones are most conveniently used clinically. It is thus important to recognize that both patented and nonpatented compounds can address unmet clinical needs, improve patient outcomes, and create significant revenues while following very different business models. I would, however, urge caution regarding exploiting the lack of patent protection for rebranding long-established compounds. Such measures would simply create market and customer confusion.

Theranostics are rapidly growing and have generated substantial interest from industry. Both protected and unprotected compounds will have their place in the clinic and in research. Non–patent-protected compounds could greatly facilitate translational research, addressing (independent of Big Pharma) resistance to PSMA-targeted therapeutics, for instance.

Protected and nonprotected compounds will give rise to larger and smaller companies, all aiming to become fiscally solid despite very different business models.

They all are part of the new nuclear medicine ecosystem, make important contributions to patient care, and will shape the further development of our discipline. We should therefore appropriately appreciate the outstanding contributions that have given nuclear medicine an immense boost over the past 15 years.

REFERENCES


18F-FDG–Avid Axillary Lymph Nodes After COVID-19 Vaccination

TO THE EDITOR: In a recent patient with a left-side parotid malignancy (biopsy-proven mammary analog secretory carcinoma), 18F-FDG PET/CT was obtained during the workup (Fig. 1). The findings showed 18F-FDG avidity in the left axillary lymph nodes with an overall SUV$_{max}$ of 4.5 and an 18F-FDG–avid left supraclavicular lymph node. This result prompted an ultrasound-guided biopsy of the lymph nodes before surgery. Pathologic examination of both subsites revealed lymphocytes consistent with a benign lymph node. Around the time of the biopsy, the patient recalled that she had received the first dose of the Moderna Therapeutics messenger RNA-1273 vaccine 10 d beforehand in her left deltoid. After vaccination, she had injection site soreness and some mild fatigue and general malaise for about 4 h. She then underwent successful superficial parotidectomy, with margin-negative and node-negative resection of the left parotid mammary analog secretory carcinoma.

Shortly after the aforementioned patient was seen, 3 mo post-treatment PET imaging was obtained as part of oncologic surveillance for a patient with a history of oral cavity/oropharyngeal squamous cell carcinoma. On physical examination 3 d before her PET study, laryngoscopy revealed findings concerning for recurrence in the previous surgical bed. Both sides of the neck were palpated, and no lymphadenopathy was appreciated. On PET, the left axillary and left supraclavicular nodes had 18F-FDG avidity, with an SUV$_{max}$ of 5.1. Because of our previous experience with the other patient, this second patient was questioned specifically regarding coronavirus disease 2019 (COVID-19) vaccination. She was able to recall that she had received the first dose of the COVID-19 vaccine 14 d beforehand, though she could not recall the manufacturer. The patient reported minimal symptoms after vaccination and was asymptomatic at the time of the PET scan. She was taken to the operating room for direct laryngoscopy, and biopsy of the concerning area revealed mild dysplasia with no evidence of carcinoma.

18F-FDG uptake is not tumor-specific and can be seen in infection, inflammation, and granulomatous disease (1). Axillary lymph node 18F-FDG avidity has been reported in patients receiving several types of vaccines, including vaccinations to influenza, H1N1, and the human papillomavirus vaccine, but has not been reported in association with the COVID-19 vaccine (2-4). Ultrasound-guided fine-needle aspiration is generally a low-morbidity procedure, though no procedure is without risk. Biopsy of her axillary node could likely have been avoided if the correlation between her recent history of vaccination and her left axillary 18F-FDG–avid lymph nodes had been determined. Limited data on mammary analog secretory carcinoma shows a 5.5% rate of cervical nodal metastasis, but biopsy of a
Supraclavicular node with 18F-FDG uptake is prudent in the setting of an ipsilateral parotid malignancy (5).

As vaccination against the 2019 novel coronavirus becomes more widespread, it will be important to consider vaccination history, especially in patients who undergo 18F-FDG PET/CT for cancer staging or surveillance. Reporting the vaccine history and injection location before obtaining PET imaging may help with interpretation of these studies. Further study could reveal what percentage of patients have 18F-FDG-avid lymph nodes after vaccination and elucidate the time required after vaccination to allow for resolution of uptake in regional lymph nodes. This information may be able to guide recommendations on the timing of PET imaging and COVID-19 vaccination.

REFERENCES


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Specific and Nonspecific Uptake in Quantitative 89Zr-Immuno-PET

TO THE EDITOR: In a recent review, van Dongen et al. illustrated why 89Zr-immuno-PET has become an important tool for the in vivo characterization of novel biologic drugs and their targets (1A). A technical “State of the Art” article summarized PET quantification of 89Zr-tracer uptake, stressing that total tissue uptake results from a target-specific and a nonspecific contribution. The latter involves a first, so-called reversible, part related to free tracer in blood and interstitium, quantified by the Patlak y-intercept (Vt). The second, irreversible, part is related to 89Zr residualization after monoclonal antibody (mAb) uptake and degradation by antigen-negative cells, quantified by the Patlak uptake-rate constant (Ki). This description is fully in line with a previous study coauthored by van Dongen, using Patlak analysis in normal tissues (kidney, liver, lung, and spleen) without known target expression for 4 89Zr-labeled mAbs, respectively (2). van Dongen et al. thus suggested that future quantitative 89Zr-immuno-PET studies should consider multiple-time-point acquisitions to assess nonspecific uptake versus time, with at least 3 late time points, and that sophisticated modeling strategies should be developed (1,2).

We believe that this suggestion warrants further comments that might be helpful for anticipating quantitative 89Zr-immuno-PET studies in tumors, designed for assessing in vivo target engagement. First, the nonspecific-irreversible uptake should be quantitatively compared with the total-tumor uptake, in order to actually determine whether it might be significant or negligible (1,2). To justify this proposal, let us consider recent results about 89Zr-anti-PD-L1, designed for monitoring in vivo chemotherapy-mediated modulation of tumor-PD-L1 expression (3). After extracting tracer input function and tumor data showing irreversible uptake (using the Web-Plot-Digitizer software in Jung et al.’s Figures 2B and 3B, respectively (3)), Patlak analysis provides a total-tumor Ki of 0.0289 mL·g⁻¹·h⁻¹ (R² = 0.9993). For comparison, combining 4 89Zr-labeled mAbs, the baseline value of the nonspecific Ki in the kidney, liver, lung, and spleen was previously found to be 0.0007, 0.0011, 0.0002, and 0.0005 mL·g⁻¹·h⁻¹, respectively (2). The total tumor Ki value of the 89Zr-anti-PD-L1 random example thus appears to be between 26- and 145-fold higher than the nonspecific Ki values of normal tissues. Even assuming that the nonspecific contribution might vary depending on tumors and patients, unlike for normal tissues across patients, we do suggest this first issue deserves consideration.

Second, we suggest that the principle of a 3-time-point method, previously described for quantitative 64Cu-immuno-PET, might be adapted to 89Zr-immuno-PET (4). Rather than the late time points suggested by van Dongen et al., 3 time points are needed at early (after reaching equilibrium), mid, and late imaging, for assessing Ki, Vt, and a release-rate constant (kR). Indeed, we believe the Patlak assumption of irreversible uptake cannot be justified in an arbitrary tissue, including tumors, as evidenced by 64Cu-NOTA-RamAb in VEGFR-2–positive HCC4006 tumors: Ki = 0.0314 mL·g⁻¹·h⁻¹, kR = 0.0387 h⁻¹, and Vt = 0.2075 mL·cm⁻³ (without a RamAb blocking dose) (4). Noteworthy, this method cannot differentiate between specific and nonspecific uptake, and the actual meaning of the 3 kinetic parameters should be specified under each situation.