Journal of Nuclear Medicine, published on January 2, 2025 as doi:10.2967/jnumed.124.268861

Gastrin-Releasing Peptide Receptor Imaging and Therapy in the Era of Personalized Medicine

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Gastrin-releasing peptide receptor (GRPR), or bombesin receptor 2, is a membrane receptor overexpressed in several solid tumors, including prostate tumors, breast tumors, gastrointestinal stromal tumors (GISTs), small cell and non–small cell lung cancer, gastrinomas, colon cancer, cervical uterine cancer, gliomas, and melanoma. This target adds to the theranostic armamentarium, as many optimized radiopharmaceuticals are becoming available.

An article by Wang et al. in *The Journal of Nuclear Medicine* shed light on GRPR imaging in GISTs (*1*). PET/CT using [^{68}Ga]Ga-NOTA-RM26, a GRPR-targeting radiopharmaceutical, detected 88.9% of the 18 pathologically confirmed GIST lesions in 16 patients, whereas [^{18}F]-FDG PET/CT detected only 50% ($P < 0.01$). SUV_{max} was substantially higher with [^{68}Ga]Ga-NOTA-RM26 than with [^{18}F]-FDG (mean, 17.07 ± 19.57 vs. 2.28 ± 1.65; $P < 0.01$) and was strongly correlated with GRPR immunostaining on immunohistochemistry. The authors found GRPR PET/CT imaging helpful in distinguishing GISTs from benign leiomyomas and schwannomas, based on a higher SUV_{max} in GISTs (*1*). These results suggest that GRPR-targeted imaging can be relevant for surgical planning and treatment decisions in selected patients. However, a heterotopic pancreas would be more difficult to differentiate from GISTs on the basis of the SUV_{max} cutoff proposed by Wang et al.

GISTs are mesenchymal tumors arising from Cajal interstitial cells within the myenteric plexus of the muscularis propria, typically in the stomach (60%), jejunum and ileum (30%), or, less frequently, the duodenum, rectum, colon, or esophagus. The mean age at diagnosis is 60–65 y, with no sex predilection. GISTs are associated with activating mutations of *KIT* (~75%), platelet-derived growth factor receptor-α (~10%), or less frequent mutations (e.g., NF-1 mutation) or deficiency in one of the succinate dehydrogenase subunits. GISTs usually present as localized disease, but recurrence and metastasis are frequent. Advanced GISTs are treated with a combination of surgery and tyrosine kinase inhibitors (TKIs) (e.g., imatinib first-line, sunitinib, regorafenib), but patients develop TKI resistance over time. High expression of GRPR and other neuropeptide receptors in primary and metastatic GISTs has been reported by Reubi et al. using receptor autoradiography, setting the basis for theranostic applications (*2*). An immunohistochemistry study found moderate or high GRPR expression in 80% of GIST primary tumors (*3*). There was no association between GRPR expression and relapse-free survival (*3*).

The results obtained with the GRPR antagonist ligand [^{68}Ga]Ga-NOTA-RM26 (*1*) show improvement over previous reports using GRPR agonist ligands (*4*). With the advent of radiolabeled antagonists, the role of GRPR imaging is now clearly emerging. However, a small phase I/IIa study (MITIGATE), which enrolled 9 patients with advanced GISTs, under current or previous TKI treatment and imaged with [^{68}Ga]Ga-NeoBOMB1 (now [^{68}Ga]Ga-NeoB), another radiolabeled GRPR antagonist, showed heterogeneous results (*5*). Tracer uptake was shown in all lesions in 3 patients, in only some lesions in 3 patients, and in no lesions in 3 patients. Tracer uptake was correlated with the absence of a necrotic appearance on CT. Contrast-enhanced CT showed higher sensitivity (86.5%) than [^{68}Ga]Ga-NeoB PET/CT (45.9%), although 5 lesions (13.5%) were identified only by [^{68}Ga]Ga-NeoB PET (*5*).

The small size and single-center design of Wang et al.'s study may limit the generalizability of the findings. Since GISTs are rare (<1% of gastrointestinal tumors), multicenter trials are needed to further investigate the potential role of GRPR imaging and assess GRPR PET/CT positivity according to tumor site of origin, tumor size, mitotic rate, National Institutes of Health risk score, mutation status, primary versus metastatic lesions (liver, peritoneal, etc.), and TKI status. Importantly, Wang's study mainly concerned primary GISTs (14 primary, 2 recurrent) and patients without (12/16) TKI treatment (*1*), whereas MITIGATE included advanced patients mostly on TKI therapy, which might explain the lower reported sensitivity (*5*). Berndsen et al. showed that moderate to high GRPR expression on immunohistochemistry was less frequent in primary GIST tumors after neoadjuvant TKI treatment (*3*). However, they did not examine samples from patients with recurrence after TKI. Studies comparing [^{68}Ga]Ga-NOTA-RM26 and [^{18}F]FDG in patients with advanced or metastatic GIST, considering TKI status (naïve, ongoing TKI therapy, resistant), are thus warranted. Additionally, whereas [^{18}F]-FDG PET showed prognostic value when assessing early response to TKI, the role of GRPR imaging in treatment response monitoring is still unknown. Other parameters to investigate include the ideal imaging time, which for [^{68}Ga]Ga-NeoB and [^{68}Ga]Ga-RM2 appears to be 2 h rather than 1 h (*5,6*). Patients were imaged with [^{68}Ga]Ga-NOTA-RM26 at about 51 min after injection (*1*).

Received Oct. 22, 2024; revision accepted Dec. 5, 2024.
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Published online Jan. 2, 2025.

DOI: 10.2967/jnumed.124.268861

Only limited therapeutic options are available for patients with unresectable or metastatic GISTs who either do not initially harbor a treatment-sensitive oncogenic mutation or develop resistance to TKI. GRPR-based targeted radiopharmaceutical therapy may constitute an option. A phase I/IIa clinical trial (NCT03872778) is investigating [^{177}Lu]Lu-NeoB in patients with various tumors, including GISTs.

There is mounting evidence that GRPR imaging and therapy could play an increasing role in precision medicine for cancer care. GRPR imaging may judiciously complement PSMA imaging in challenging cases of PSMA-low prostate cancer lesions. Representative examples include low-grade localized prostate cancer (*6*), which in turn served as a molecular basis for guiding biopsy and local treatments, as reported by the Iagaru group at Stanford. In biochemical recurrent prostate cancer, GRPR PET can be complementary to PSMA imaging, and the profile of GRPR-positive patients is being investigated (*7*). A first-in-human study with [^{177}Lu]Lu-RM2 showed high absorbed doses to prostate cancer metastases (*8*). Compared with PSMA-targeted radiopharmaceutical therapy, the absence of GRPR expression in salivary glands is advantageous, although the impact of high GRPR expression in the pancreas deserves specific consideration. Interestingly, despite high initial uptake, some radioligands show faster decline in the pancreas than in tumor lesions, with favorable tumor-to-pancreas uptake ratios on late imaging. The phase I/IIa clinical trial COMBAT is investigating [^{67}Cu]Cu-SAR-BBN in prostate cancer patients ineligible for [^{177}Lu]Lu-PSMA-617 therapy (NCT05633160). GRPR has been detected at high frequency in estrogen receptor–positive breast cancer (*9*). GRPR imaging might play a role when [^{18}F]-FDG shows relatively low uptake, such as in lobular carcinoma or low-grade tumors, and deserves comparison to [^{18}F]-FES and fibroblast activation protein–targeted radiopharmaceuticals. [^{177}Lu]Lu-NeoB is now being investigated in combination with ribociclib and fulvestrant (NCT05870579), or with capecitabine (NCT06247995), in metastatic breast cancer after progression on endocrine therapy plus a CDK4/6 inhibitor. The α-emitting [^{212}Pb]Pb-DOTAM-GRPR1 is being investigated in various GRPR-expressing metastatic tumors, including estrogen receptor–positive breast cancer (NCT05283330).

Finally, whereas somatostatin receptor antagonists are now widely investigated, GRPR is an exemplary case for antagonist-based radiopharmaceuticals. For targeted radiopharmaceutical therapy, GRPR antagonists hold additional significant advantages over agonists, including the avoidance of some gastrointestinal side effects and the potential risk of stimulatory effects on tumor growth. The lack of internalization of antagonists has previously been considered a limitation. However, the strong uptake and prolonged retention on tumor cells, along with a potential role in cell membrane irradiation, are now being explored. Some radionuclides emitting Auger electrons, such as ^{161}Tb, may be particularly suited for attaching to antagonists residing at the cell surface, delivering high doses to tumor cell membranes in addition to cell nuclei (*10*). A clinical trial is currently investigating the somatostatin receptor antagonist ^{161}Tb-DOTA-LM3 (NCT05359146), based on preclinical results. As of now, ^{161}Tb-labeled GRPR antagonists ([^{161}Tb]Tb-RM2 and [^{161}Tb]Tb-AMTG) have only been investigated preclinically. Clinical trials are eagerly awaited. The benefit of using antagonists for targeting could indeed extend to many other G-protein–coupled receptors.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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