^{68}Ga/^{177}Lu-NeoBOMB1, a Novel Radiolabeled GRPR Antagonist for Theranostic Use in Oncology

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Because overexpression of the gastrin-releasing peptide receptor (GRPR) has been reported on various cancer types, for example, prostate cancer and breast cancer, targeting this receptor with radioligands might have a significant impact on staging and treatment of GRPR-expressing tumors. NeoBOMB1 is a novel DOTA-coupled GRPR antagonist with high affinity for GRPR and excellent in vivo stability. The purpose of this preclinical study was to further explore the use of NeoBOMB1 for theranostic application by determining the biodistribution of ^{68}Ga-NeoBOMB1 and ^{177}Lu-NeoBOMB1. **Methods:** PC-3 tumor–xenografted BALB/c *nu/nu* mice were injected with either approximately 13 MBq/250 pmol ^{68}Ga-NeoBOMB1 or a low (~1 MBq/200 pmol) versus high (~1 MBq/10 pmol) peptide amount of ^{177}Lu-NeoBOMB1, after which biodistribution and imaging studies were performed. At 6 time points (15, 30, 60, 120, 240, and 360 min for ^{68}Ga-NeoBOMB1 and 1, 4, 24, 48, 96, and 168 h for ^{177}Lu-NeoBOMB1) postinjection tumor and organ uptake was determined. To assess receptor specificity, additional groups of animals were coinjected with an excess of unlabeled NeoBOMB1. Results of the biodistribution studies were used to determine pharmacokinetics and dosimetry. Furthermore, PET/CT and SPECT/MRI were performed. **Results:** Injection of approximately 250 pmol ^{68}Ga-NeoBOMB1 resulted in a tumor and pancreas uptake of 12.4 ± 2.3 and 22.7 ± 3.3 percentage injected dose per gram (%ID/g) of tissue, respectively, at 120 min after injection. ^{177}Lu-NeoBOMB1 biodistribution studies revealed a higher tumor uptake (17.9 ± 3.3 vs. 11.6 ± 1.3 %ID/g of tissue at 240 min after injection) and a lower pancreatic uptake (19.8 ± 6.9 vs. 105 ± 13 %ID/g of tissue at 240 min after injection) with the higher peptide amount injected, leading to a significant increase in the absorbed dose to the tumor versus the pancreas (200 pmol, 570 vs. 265 mGy/MBq; 10 pmol, 435 vs. 1393 mGy/MBq). Using these data to predict patient dosimetry, we found a kidney, pancreas, and liver exposure of 0.10, 0.65, and 0.06 mGy/MBq, respectively. Imaging studies resulted in good visualization of the tumor with both ^{68}Ga-NeoBOMB1 and ^{177}Lu-NeoBOMB1. **Conclusion:** Our findings indicate that ^{68}Ga- or ^{177}Lu-labeled NeoBOMB1 is a promising radiotracer with excellent tumor uptake and favorable pharmacokinetics for imaging and therapy of GRPR-expressing tumors.

Key Words: cancer theranostics; gastrin releasing peptide receptor; GRPR antagonist; biodistribution; dosimetry

J Nucl Med 2017; 58:293–299
DOI: 10.2967/jnumed.116.176636

The gastrin-releasing peptide receptor (GRPR), also known as bombesin receptor subtype 2, is a G-protein–coupled receptor expressed in various organs, including those of the gastrointestinal tract and the pancreas (*1,2*). On binding of a suitable ligand, the GRPR is activated, eliciting multiple physiologic processes, such as regulation of exocrine and endocrine secretion (*1,2*). In the past decades, GRPR expression has been reported in various cancer types, including prostate cancer and breast cancer (*3,4*). Therefore, the GRPR became an interesting target for receptor-mediated tumor imaging and treatment, such as peptide receptor scintigraphy and peptide receptor radionuclide therapy (*2*). After the successful use of radiolabeled somatostatin peptide analogs in neuroendocrine tumors for nuclear imaging and therapy (*5,6*), multiple radiolabeled GRPR radioligands have been synthesized and studied in preclinical as well as in clinical studies, mostly in prostate cancer patients. Examples of such peptide analogs include AMBA, the Demobesin series, and MP2653 (*7–11*). Recent studies have shown a preference for GRPR antagonists compared with GRPR agonists (*12,13*). Compared with receptor agonists, antagonists often show higher binding and favorable pharmacokinetics (*14*). Also, clinical studies with radiolabeled GRPR agonists reported unwanted side effects in patients caused by activation of the GRPR after binding of the peptide to the receptor (*15*).

Although imaging and treatment with radiolabeled GRPR peptide analogs is not yet approved for routine clinical practice,