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The emergence of somatostatin antagonist-based theranostics: Paving the road toward another success?

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The value of *in vivo* peptide receptor targeting for imaging and treating oncologic patients is well accepted and implemented in clinical practice. A prime example is somatostatin receptor (SSTR)-targeted peptide receptor radionuclide therapy (PRRT), which relies on an 'image and treat' approach (theranostics), a rapidly evolving clinical concept in patients with neuroendocrine tumors (NETs).

SSTR-agonists are internalized following high affinity ligand-receptor binding and have historically been used for *in vivo* SSTR receptor targeting. This mechanism is considered an essential step in the *in vivo* receptor targeting using SSTR-agonists (Figure 1). The evolving PET/CT technology and the optimization of radiopharmaceutical chelation for effective somatostatin analog development opened the door to [^{68}Ga]Ga-DOTA(0)-Tyr(3)-octreotate ([^{68}Ga]Ga-DOTATATE) PET/CT. In 2016, [^{68}Ga]Ga-DOTATATE received the FDA approval for SSTR imaging, followed by [^{68}Ga]Ga-DOTATOC and [^{64}Cu]Cu-DOTATATE in 2019 and 2020, respectively. SSTR-based PRRT was explored by Phase-3 NETTER-1 trial, a first time-in-humans prospective multicenter randomized clinical trial comparing [^{177}Lu]Lu-DOTATATE (4 cycles, 7.4 GBq/cycle) to high-dose octreotide in 229 patients with progressive low-grade midgut NETs.

The NETTER-1 trial significantly improved progression-free survival (PFS) with [^{177}Lu]Lu-DOTATATE, with a hazard ratio (HR) of 0.18 (95%CI: 0.11–0.29, $p<0.0001$) (1). However, five years after the last patient randomization, there was no statistically significant difference in the median overall survival (OS) between the [^{177}Lu]Lu-DOTATATE arm (48 months; 95%CI: 37.4–55.2) and the control arm (36.3 months, 95%CI: 25.9–51.7) despite a clinically significant improvement of the quality of life and PFS in [^{177}Lu]Lu-DOTATATE arm (1). Concerning the treatment safety, only 3/111 patients (3%) of [^{177}Lu]Lu-DOTATATE arm showed treatment-related severe adverse events during long-term follow-up, and two patients (2%) developed myelodysplastic syndrome, one of whom died 33-months after randomization. No new cases of myelodysplastic syndrome or acute myeloid leukemia were reported during long-term follow-up. At present, the NETTER-2 trial is ongoing to determine whether [^{177}Lu]Lu-DOTATATE prolongs PFS in grade-2/3 gastroenteropancreatic NETs as first-line treatment in combination with long-acting octreotide (NCT03972488). A recent meta-analysis including more than 1,200 patients treated by [^{177}Lu]Lu-DOTATATE (1-8 cycles, 3.7-10 GBq/cycle), revealed a disease control rate [proportion of complete response (CR), partial response (PR), minor response (MR), and stable disease] of 74.1% (95%CI: 67.8%–80%) and a disease response rate (proportion

of CR, PR, and MR) of 29.1% (95% CI: 20.2%–38.9%) (2). This evidence contributed to the inclusion of [^{177}Lu]Lu-DOTATATE in the therapeutic algorithms proposed by leading international societies as an effective and safe treatment option for NETs. Recently, a novel SSTR-agonist radioligand, [^{64}Cu]^{64}Cu-SARTATE, was compared to [^{68}Ga]Ga-DOTATATE showing higher uptake and retention resulting in high-contrast diagnostic images upwards of 24-hours (3). [^{67}Cu]Cu-SARTATE, the therapeutic counterpart of [^{64}Cu]Cu-SARTATE is currently being evaluated (NCT04023331).

Over the years, novel data has emerged for SSTR-antagonists. The application of SSTR-antagonists was initially discouraged due to lack of internalization. Despite these initial considerations, it was later found that a higher percentage of SSTR antagonists were bound compared to agonists in animal and human models. This can be mainly attributed to the functional interaction of SSTR antagonists with a larger variety of SSTR conformations, allowing binding both activated and inactivated SSTRs (4,5) (Figure 1). Slow dissociation of antagonist-receptor binding and minimal internalization are also thought to play a role in tumor detection. Further, SSTR-antagonists are more chemically stable and hydrophobic than SSTR-agonists, with a consequent longer duration of action and stabilization in a lipid-rich environment (4).

From a theranostic point of view, the high target-to-background ratio and the prolonged *in vivo* tumor binding obtained with radiolabeled SSTR-antagonist have been of paramount importance in promoting the use of SSTR-antagonists over SSTR-agonists. Compared to [^{68}Ga]Ga-DOTATATE in NETs, both [^{68}Ga]Ga-NODAGA-LM3 and [^{68}Ga]Ga-DOTA-LM3 demonstrated a significantly higher detection of liver metastases (202 vs 235, p=0.01 and 196 vs 261, p=0.02, respectively) and overall lesions (339 vs 395, p=0.002 and 372 vs 447, p=0.02, respectively) with higher tumor-to-liver ratio of matched lesions in both arms (p=0.00). There was no significant difference in detection of primary tumors (17 vs 19, p=0.16 and 13 vs 15, p=0.16, respectively), lymph node metastases (24 vs 27, p=0.18 and 29 vs 32, p=0.18, respectively), bone metastases (31 vs 46, p=0.11 and 126 vs 126, p=1.00, respectively), or other lesions (65 vs 68, p=0.32 and 8 vs 13, p=0.10, respectively) (6). In another comparative study, [^{68}Ga]Ga-DOTA-JR11 detected more liver (552 vs 365, p=0.001) but fewer bone (158 vs 388, p=0.02) metastases than ^{68}Ga-DOTATATE, but with comparable primary tumor detection (20 vs 24, p=0.50) and overall detection rate (835 vs 875, p=0.15), and with equal lymph node (43 vs 43), pleural (51 vs 51), and peritoneal (2 vs 2) metastases (7). Similarly, in 12 gastroenteropancreatic NETs patients, [^{68}Ga]Ga-

NODAGA-JR11 demonstrated a significantly higher overall sensitivity (94% with 50 μg and 88% with 15 μg of [^{68}Ga]Ga-NODAGA-JR11 compared to [^{68}Ga]Ga-DOTATOC (15 μg, 59.2%, $p<0.001$ for both doses of [^{68}Ga]Ga-NODAGA-JR11) (8).

Radioligand SSTR-antagonists have been documented to bind a higher percentage of SSTRs than agonists (Figure 1), which increases targeting even for tumors with low SSTR expression (4,5). This would be clinically important in high-grade NETs, poorly-differentiated neuroendocrine carcinoma, and certain non-NETs (breast carcinomas, renal cell carcinomas, and non-Hodgkin lymphomas) (9). For these reasons, there has been increasing interest in SSTR-antagonists. In humans, two theranostic pairs of JR11 (i.e.: [^{68}Ga]Ga-DOTA-JR11/[^{177}Lu]Lu-DOTA-JR11, [^{68}Ga]Ga-NODAGA-JR11/[^{177}Lu]Lu-DOTA-JR11) have already been investigated (10,11). However, the safety profile of SSTR-antagonists for PRRT requires further consideration and optimization. Severe hematotoxicity was observed compared to SSTR-agonists at doses equivalent/greater to red marrow. In a recent phase-I clinical trial (12), 4/4 patients who received two cycles of [^{177}Lu]Lu-satoreotide-tetraxetan (also known as [^{177}Lu]Lu-DOTA-JR11) and an estimated bone marrow dose ≥1.44 Gy developed G4 thrombocytopenia (and G3/4 neutropenia) and 57% developed G4 myelosuppression but none of the patient with ≤ 1.08 Gy bone marrow dose experienced G4 thrombocytopenia or neutropenia. Therefore, the therapeutic protocol was revised to lower the bone marrow dose from 1.5 to 1 Gy and subsequently, halve the dose in cycle two. However, the hypothesis that the activity concentration in the red marrow is comparable to that in blood (11) could be probably reconsidered, as SSTR antagonists may have specific binding in the red marrow, also supporting a dedicated dosimetry based on post-therapeutic SPECT/CT imaging.

[^{68}Ga]Ga-DOTA/NODAGA-LM3 and [^{177}Lu]Lu-DOTA-LM3 represent another attractive SSTR-antagonist based theranostic pair with high tumor binding and preliminary favorable dosimetry (13). Furthermore, radiolabeling of SSTR-antagonists with α-emitters would provide a joint benefit from the biological characteristics of the antagonists and the physical properties of the α-emitters, with potential therapeutic advantages even in patients refractory to treatment with β-emitter-labeled somatostatin analogs.

In conclusion, published literature strongly suggests that SSTR-antagonists are characterized by no cellular internalization but a strong binding capacity to SSTR receptors, suggesting a higher efficacy than SSTR-agonists that undergo cellular internalization and have

weaker SSTR binding. These unique characteristics of SSTR-antagonists are now shifting clinical focus towards the use of radiolabeled SSTR-antagonists to improve diagnostic sensitivity (with some concerns at the bone level (7)) and therapeutic efficacy of SSTR-based PRRT. While SSTR-antagonists have been optimized at the diagnostic level, therapeutic applications must be further investigated. Decreasing administered activities, encouraging dosimetry, and increasing duration between PRRT cycles in order to limit hematotoxicity while preserving therapeutic efficacy should be further researched. Patients with multiple liver metastases and those with poorly differentiated NETs could be suitable candidates for promising new clinical investigations. Thus, SSTR-antagonists currently represent a novel paradigm in theranostics that will undoubtedly revolutionize diagnostic and therapeutic management of NETs. We hope these discoveries will ultimately improve the clinical outcomes of patients with these rare tumors.

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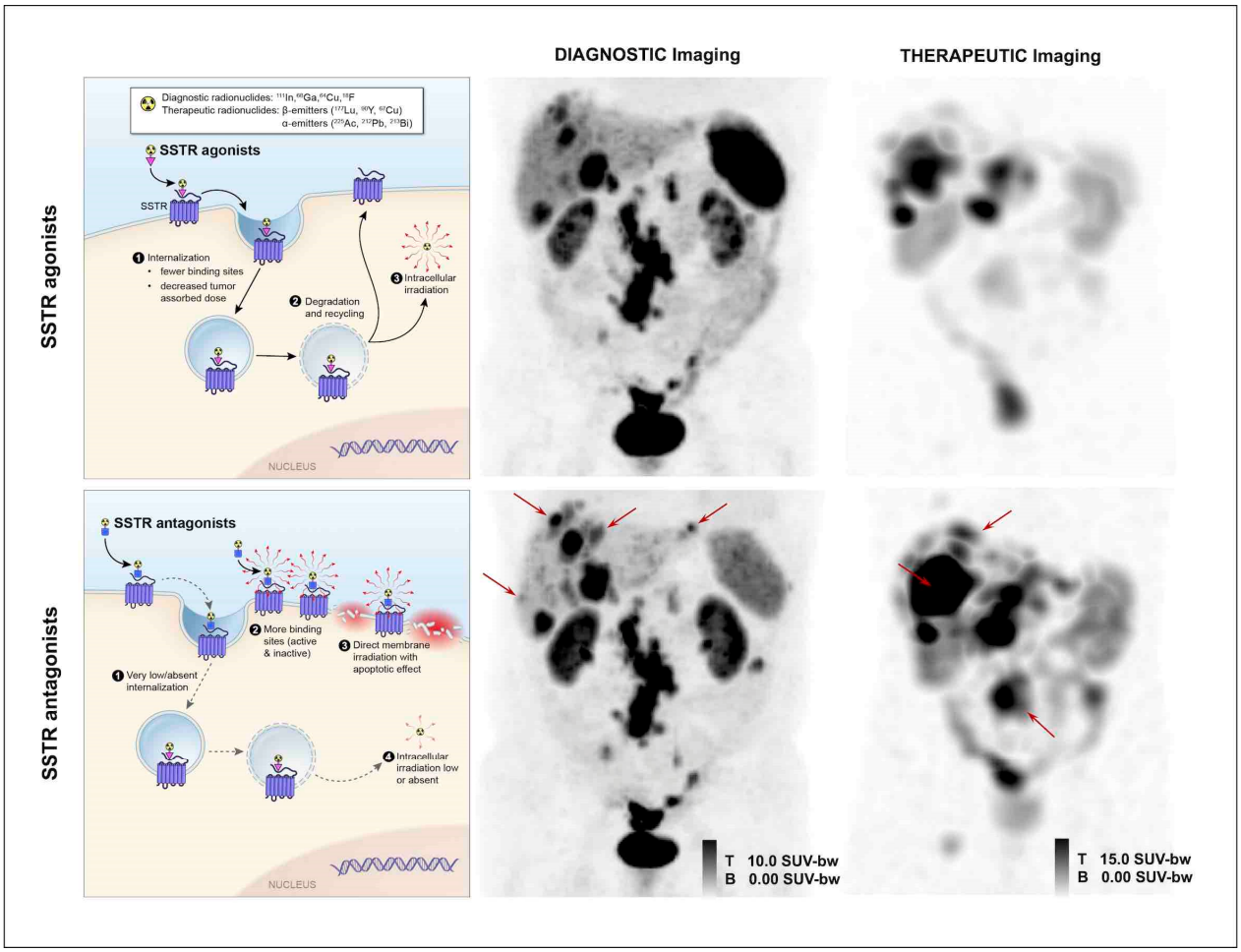

FIGURE 1. *Left column:* mechanism of action of radiolabeled SSTR-agonists and antagonists for theranostics application. SSTR-agonists are internalized after binding to the SSTR2 with consequent accumulation of radioactivity in the cell. On the contrary, the SSTR-antagonists bind more effectively to receptors on the cell membrane with almost absent internalization and direct membrane damage. *Middle column:* Head-to-head comparison between PET images (anterior MIP, SUVmax range: 0-10) of [^{68}Ga]Ga-DOTATOC (SSTR-agonist) and [^{68}Ga]Ga-NODAGA-JR11 (SSTR-antagonist) in a patient with low-grade NET, showing more lesions (arrows, particularly in the liver) for [^{68}Ga]Ga-NODAGA-JR11 compared to [^{68}Ga]Ga-DOTATOC. *Right column:* direct comparison of post-treatment SPECT images (anterior MIP, SUVmax range: 0-15) after [^{177}Lu]Lu-DOTATOC (cycle-1) and [^{177}Lu]Lu-DOTA-JR11 (cycle-2) performed within a ten weeks interval. Tumor activity concentration at 24h p.i. is ~30% higher with the antagonist (arrows) than with the agonist even though the administered activity of Lu-177 is ~50% less for the antagonist compared to the agonist (3.9 GBq vs 7.4 GBq).