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EDITORIAL

Is Peptide Receptor Radionuclide Therapy on the Horizon for Unresectable or Metastatic Gastroenteropancreatic Neuroendocrine Tumours?

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With their insidious onset and indolent clinical behaviours,[1] unresectable or metastatic neuroendocrine tumours (NETs) have long been regarded as one of the most intractable malignancies. The digestive system is the most common site of involvement. In particular, the gastroenteropancreatic (GEP) location of NETs (GEP-NETs) as the most common well-differentiated NET has been of great interest to clinicians. Well-differentiated NETs are classified into grade 1 (Ki-67 index <3%), grade 2 (Ki-67 index 3-20%), and grade 3 (Ki-67 index >20%).[2] The abundant expression of somatostatin receptors (SSRTs), especially subtype 2 (SSRT2) on the NET cell surface makes SSRT-directed therapy a promising treatment option.[3,4]

Traditionally, somatostatin analogues, including octreotide, lanreotide, and pasireotide, alone or in combination with targeted therapy, have been the most commonly used treatments for unresectable or metastatic NETs, showing durable and effective tumour control with favourable safety profiles.[5-7] Most recently, peptide receptor radionuclide therapy (PRRT) with either lutetium-177 (^{177}Lu) or yttrium-90 has established itself as a safe and effective treatment for unresectable or metastatic GEP-NETs.[5] The NETTER-1 study, which compared ^{177}Lu-dotatate plus standard-dose long-acting octreotide to high-dose long-acting octreotide alone as second-line therapy in patients with advanced midgut NETs demonstrated a significantly higher objective response to ^{177}Lu-dotatate and a better progression-free survival (PFS), although the secondary endpoint of overall survival (OS) was not met.[8,9] In view of such encouraging result using ^{177}Lu-dotatate PRRT as second-line treatment, the NETTER-2 study was subsequently conducted to evaluate the efficacy and safety of first-line ^{177}Lu-dotatate PRRT plus long-acting repeatable (LAR) octreotide versus high-dose LAR octreotide alone in patients with higher grade 2 (Ki-67 indices ≥10% and ≤20%) and grade 3 (Ki-67 indices >20% and ≤55%) NETs.[10] The results again demonstrated a better objective response (43% vs. 9%) and longer PFS (22.8 months vs. 8.5 months; hazard ratio 0.28, $p < 0.0001$) but not a lengthened OS, when compared to LAR indium-111 octreotide (^{111}In-octreotide) alone.[10] The absence of a significant OS benefit is often observed in cross-over studies, where patients in the control group may later receive investigational treatment. It should be noted that almost all published studies have mainly recruited Caucasians. The efficacy and safety of PRRT has been less well assessed in the Chinese population.

Wong et al[11] reported the outcomes of PRRT in their retrospective study of 21 Chinese patients with metastatic NETs treated in a single institution in Hong Kong, including one patient who had grade 3 NET. Most of them (85.7%) had received at least one prior line of systemic therapy, including somatostatin analogues, targeted therapy, and/or chemotherapy, while

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the remaining three patients (14.3%) received PRRT as their first-line systemic treatment. All patients had undergone ^{111}In-octreotide scintigraphy or gallium-68 dotatate (^{68}Ga-dotatate) positron emission tomography with computed tomography (PET/CT) scanning prior to treatment, which confirmed that the amount of SSRT uptake by tumour cells was equal to or greater than that of normal tissues. Both ^{177}Lu and yttrium-90 were used in two patients. The recruited patients underwent an average of four PRRT sessions, ranging from one to six sessions.

The study by Wong et al[11] reported an objective response rate of 47.6% was observed, in addition to 23.8% stable disease. The median PFS and OS were 22.3 months and 45.2 months, respectively, after a median follow-up duration of 19.0 months. Multivariable analysis revealed that bone metastasis and a high liver tumour burden of more than 50% were significant negative prognostic factors in OS. Lymphopenia, followed by anaemia, neutropenia, thrombocytopenia, and hepatotoxicity were the most common adverse events after PRRT. Grade 3/4 toxicities with lymphopoenia and hepatotoxicity were reported in 42.9% and 4.8% of patients, respectively. Of interest, two patients received retreatment with PRRT after their initial courses of PRRT, with tolerable and manageable grade 3 lymphopenia noted in one patient. No patient developed myelodysplastic syndrome, which had been seen in one patient who had this possibly PRRT-related toxicity approximately 14 months after the first dose of PRRT in the NETTER-2 study.[10]

Despite the relatively small number of patients and retrospective nature of this study, Wong et al[11] demonstrated for the first time that PRRT is a safe and effective treatment for metastatic GEP-NETs in a Chinese population, echoing the results of the NETTER-1[8,9] and NETTER-2 trials.[10] Patient selection and eligibility screening based on the uptake of ^{111}In-octreotide in octreotide scintigraphy or ^{68}Ga-dotatate in ^{68}Ga-dotatate PET/CT scans may merit discussion. The Krenning score, a semi-quantitative tool, is commonly used to assess SSRT uptake based on octreotide scintigraphy and is defined as follows[12]: Grade 1 as uptake less than normal liver background activity; grade 2 as uptake equal to normal liver background activity; grade 3 as uptake greater than normal liver background activity; and grade 4 as uptake greater than spleen or kidney background activity. In the NETTER-1 study,[9] pretreatment screening was performed using octreotide scintigraphy and the Krenning score, with patients eligible if their score was grade 2, 3, or 4. The NETTER-2 study,[10] used either ^{111}In-octreotide scintigraphy with the Krenning score or ^{68}Ga-dotatate PET/CT with a modified Krenning score (an adaptation of the original Krenning score applied to ^{68}Ga-dotatate PET/CT) for eligibility. However, it is still unclear whether the modified Krenning scores are equivalent between these imaging modalities. A post-hoc head-to-head comparison study of ^{68}Ga-dotatate PET/CT and ^{111}In-octreotide scan-based Krenning scores in 150 patients from a phase 2 prospective study (NCT01967537) revealed that the Krenning score was significantly higher with PET/CT than with two-dimensional scintigraphy or ^{111}In-octreotide scintigraphy.[13] In patients with a Krenning score of 3 or above on PET/CT, the detection rates of two-dimensional scintigraphy and ^{111}In-octreotide scintigraphy were significantly lower for lesions smaller than 2 cm compared to lesions of 2 cm or larger: 15% and 24% versus 78% and 89%, respectively ($p < 0.001$). On the other hand, for lesions greater than 5 cm, the Krenning scores between PET/CT scan and octreotide scintigraphy were comparable. Lesion size did not affect PET/CT-based Krenning scores. In other words, octreotide scintigraphy may miss smaller lesions (<2 cm) that would otherwise be detected on ^{68}Ga-dotatate PET/CT. Prospective studies are warranted to standardise the use of a single imaging modality for eligibility screening.

Of concern, a recent notification was announced by the drug sponsor of the NETTER-2 study that the application for using ^{177}Lu-PRRT as first-line systemic therapy to the European Medicines Agency was withdrawn.[14] The lack of OS prolongation because of immature OS data and potentially unfavourable risks including myelodysplastic syndrome, radiation-associated second malignancies, and haematological and renal toxicities in a treatment-naïve population were the key concerns.[10] For now, the current European Medicines Agency approval for ^{177}Lu-dotatate is confined to advanced, progressive, grade 1 and grade 2 GEP-NETs.[15] Patients with grade 3 NETs are still denied access to PRRT.

In summary, PRRT is a novel and promising treatment modality for grade 1 and 2 unresectable or metastatic GEP-NETs after failure of prior systemic therapy. More prospective and mature data for grade 3 NETs and OS are awaited to confirm whether PRRT can also work favourably in this histological subgroup and as first-line therapy for treatment-naïve patients.

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