Peptide receptor radionuclide therapy after NETTER-1 clinical trial: what should not be left behind

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Background

Peptide receptor radionuclide therapy (PRRT) is an established therapy that takes advantage of the over-expression of somatostatin receptors (SSTRs) on neuroendocrine tumor cell surface, to vehicle radioactivity on cancer tissues. Approximately 80% of neuroendocrine tumors (NETs) express SSTRs on cell surface, both in primary and in related metastases. PRRT exploits this peculiarity and consists in the systemic administration of a synthetic analog of somatostatin incorporating a suitable beta-emitting radionuclide, which, once internalized through a specific receptor, irradiates tumor tissue. Through the years, several radioactive compounds have been proposed for functional studies and therapy of NETs and they differ for radionuclide, somatostatin analog, chelator and, consequently, also for receptors' affinity.

Over the last decades it has been shown that PRRT has promising treatment results; PRRT has been studied in numerous single-arm clinical trials, until 2017, when the preliminary results of the first multicenter, stratified, open, randomized, controlled, two-arm, Phase III clinical trial were published. The NETTER-1 study counterposed PRRT plus best supportive care, including octreotide long-acting repeatable (LAR), versus the administration of high dose of the “cold” somatostatin analog octreotide (LAR) alone. NETTER-1 PRRT was performed using ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate (DOTATATE) in a population with well-differentiated, metastatic neuroendocrine tumors of the midgut. The interim analysis reported a markedly longer progression-free survival and significantly higher response

rate with ¹⁷⁷Lu-DOTATATE than high-dose octreotide LAR. The overall survival improvement was associated with a significant benefit in terms of quality of life (QoL) compared with high-dose octreotide [1].

Following this publication, the international scientific community has developed increasing interest in PRRT and the therapy has been approved by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and National Institute for Health and Care Excellence, initiating a paradigm shift in NET treatment. Particularly, ¹⁷⁷Lu-DOTATATE (Lutathera—¹⁷⁷Lu-oxodotreotide) administration has been approved in SSTRs-positive well-differentiated gastroenteropancreatic (GEP) NETs, at a recommended fixed dosage of 7.4 GBq (200 mCi) every 8 weeks, for a total of four cycles. Whereas this represents an important milestone in the field of radionuclide therapy, some crucial points must still be addressed.

Extension of application

First of all, it must not be forgotten that PRRT and functional imaging with labeled SSAs have been effectively applied for diagnosis and treatment of several SSTRs-expressing tumors. Beyond current applications, other PRRT potential targets in oncology include meningioma, bronchial NET (small cell lung cancer as well), malignant pheochromocytoma and paraganglioma, medullary thyroid cancer and neuroblastoma [2, 3].

Apart from neuroendocrine tumors arising from GEP tract, the majority of NETs occur in the lung and bronchi. While surgery is frequently curative, this disease is usually chemo- and radio-resistant, thus limited therapeutic options are available in case of metastatic or unresectable tumors, with poor prognosis and no standard approaches. In this scenario, PRRT has shown to achieve good objective response rate and survival, decreasing biomarker levels and improving symptom control [2].

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Applications of PRRT in paraganglioma treatment have been assessed in several small cohorts of patients with inoperable disease, with promising outcomes in tumor response and symptoms' control (decreased medication requirements).

It has been proven that PRRT is an effective treatment also in case of refractory or relapsed high-risk neuroblastoma [3], offering clinicians a valid therapeutic option when chemotherapy and ^{131}I -metaiodobenzylguanidine treatment are unfeasible.

Since PRRT efficacy is related to the Ki67 index, and consequently WHO tumor grading, a subgroup of patients usually overlooked when discussing PRRT is the grade 3 neuroendocrine neoplasms (NEN) population. However, few reports show an early and sustained response after PRRT, in selected clusters of G3 NEN patients. PRRT could widen the therapeutic options and management opportunities of a subgroup of well-differentiated G3 NEN patients, usually characterized by poor prognosis [4].

Personalized treatment

Another point of discussion that arises is the personalization of PRRT. ^{177}Lu -DOTATATE has been approved at fixed dosage of 7.4 GBq per administration. In the last decade, several attempts to include dosimetric calculation in PRRT pathway have been made, but still limited data are available and consensus has not been reached [5]. Even though high rates of complete response are still quite far, the majority of patients who undergo PRRT experience disease control and improvement of QoL. Therefore optimizing treatment, with individual tailored PRRT, would translate in an extension of a patients' life expectancy and in relative good health.

Furthermore, individualizing PRRT, based on lesions' and critical organs' dosimetry on SPECT imaging, usually allows a higher number of ^{177}Lu -DOTATATE administrations. Keeping an eye on the maximum tolerated dose of the organs at risk, dosimetry ensures to safely maximize the quantity of radiation delivered to target lesions [2]. If properly explored, dosimetry would answer a few open questions about PRRT, i.e., which are the maximum tolerated dose of organs at risk, the threshold for disease response, the number of administrations to safely perform. The fundamental prerequisites for PRRT success include demonstration of high tumor uptake compared to non-target tissues and stable bone marrow and renal functions. On these bases, re-treatment should be a feasible option as well.

As a matter of fact, the possibility to continue PRRT after the fourth cycle should not be excluded a priori. Despite the durable response to radionuclide therapy, most patients experience disease progression. Additional cycles of PRRT, performed usually, but not exclusively, after progression

appear to be a safe option, however associated with a lower tumor response compared with initial treatment [6]. Toxicity prevalence does not increase compared to first PRRT treatment and, when considered as salvage therapy, PRRT is a potential treatment chance in patients that have experienced an adequate response after initial cycles [7].

A further issue in posology regards the route of administration. ^{177}Lu -DOTATATE is currently approved for intravenous delivery, but selective hepatic intra-arterial administration results in a higher uptake of radioactivity in liver metastases with a potentially consequent higher effectiveness in liver-dominant diseases [2]. Since hepatic tumor involvement is often a life-limiting factor, the possibility to improve the loco-regional response should not be underestimated.

Therapy associations

PRRT should not be considered a stand-alone therapy, its association with innovative therapeutic agents should be, indeed, actively investigated. The therapeutic action of PRRT relies on breaking the single-strand DNA, therefore, the combination with chemotherapeutics that inhibit DNA repair might enhance its efficacy. It has been recently shown in vitro that olaparib, a polymerase inhibitor, sensitizes neuroendocrine tumors' cells to PRRT. Another mechanism to be exploited should be the enhancement of antitumor immune response following PRRT, opening the door to immunotherapeutic drugs and PRRT associations [6].

PRRT beyond ^{177}Lu -DOTATATE

The strength of radio-labeled SSAs agonists is further being investigated by the COMPETE Phase III clinical trial (NCT03049189). This study is currently recruiting and will compare the efficacy of ^{177}Lu -DOTATOC versus everolimus in an estimated population of 300 patients with inoperable, well-differentiated, SSTR-positive, and progressive GEP-NET. By investigating the potential of PRRT against an active NET treatment, the clinical trial aims to move a step forward from NETTER-1.

In recent years, great interest has been shown in PRRT with alpha particle-emitting radionuclides (Bismuth-213 or Actinium-225) and in PRRT agents based on SSTR antagonists. The first procedure exploits the emission of high-energy and short-range particles that allow precisely targeted therapy, avoiding the irradiation of normal tissues [7], the latter, exploits SSTR antagonists capacity to occupy more binding sites with lower dissociation rate than agonists. Despite minimal or no internalization of the antagonist-receptor complex into tumor cells, SSTRs antagonists,

PRRT has shown preliminary efficacy data. Compared to agonists, these radiopharmaceuticals present higher tumor uptake, longer retention time on tumor tissues and shorter retention of radioactivity in healthy organs [6]. Labeled SSTRs antagonists undergoing trial are ^{111}In -DOTA-SST-ANT, ^{177}Lu -DOTA-BASS and ^{177}Lu -OPS201 (^{177}Lu -DOTAJR11 clinical trial nr. NCT02609737). These procedures are being currently studied in several clinical trials, but data are still very preliminary and go beyond the purposes of this dissertation.

Conclusions

From a global point of view, in terms of health, social and economic costs, the initial selection of patients who are likely to benefit from a specific PRRT treatment is an essential issue in clinical practice. At the same time, the optimization of novel PRRT treatments, to achieve the best possible results, may represent a great advantage in terms of toxicity and reduction in health costs.

Surfing the great expectations fed by NETTER-1 results, further advances in PRRT should be embraced. This first accomplishment should not be considered as a finish line, but a new start towards the future of personalized medicine. In this perspective, the improvement and diffusion of the dosimetric methodology, the evolvement of techniques such as the selective intra-arterial administration of radioactive peptides, along with further researches on SSAs antagonists and on different labeling nuclides, the association with chemotherapeutic or immunotherapeutic drugs are advocated.

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Compliance with ethical standards

Conflict of interest Marco Maccauro, Antonella Capozza and Ettore Seregni declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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