Supportive Measures and Finer Practice Points in ^{177}Lu-DOTATATE PRRT for NET: Aiming for Optimal Disease Management

TO THE EDITOR: Peptide receptor radionuclide therapy (PRRT) has gained substantial popularity and is now among the frequently considered options for the management of advanced neuroendocrine tumors (NETs) (*1*). Although the work-up and treatment protocol are now quite standard in most practicing centers, the attending nuclear medicine specialist should be well versed in some of the finer aspects associated with this form of therapy for bettering overall management. Herein, we address and share our own experience and thoughts on certain relevant points pertaining to PRRT practice.

Antiemetic Protocol. Nausea and vomiting related to PRRT are primarily due to metabolic acidosis related to coinfusion of a positively charged amino acid (administered to competitively block the megalin-cubilin pathway–based proximal renal tubular reabsorption of the radiopeptide). In our experience, a combination of ondansetron and corticosteroid is most effective and should be administered intravenously on a routine basis before the therapy. It is superior in reducing the incidence of emetic tendency as compared with a single agent. This protocol is already in place for chemotherapy and during anesthesia and thus could be routinely adopted safely during PRRT.

Management and Preparation of a Symptomatic Patient. Although there exists some practice diversity regarding withdrawal of long-acting somatostatin analogs before PRRT, most centers follow a withdrawal period of at least 4 wk; highly symptomatic patients, especially those in their initial few cycles of PRRT, would need short-acting formulations of octreotide administered through subcutaneous injection (100 μg 2–3 times a day) until 1 d before the therapy. After a cycle of PRRT, symptomatic patients could be given long-acting preparations monthly until 1 mo before the next scheduled PRRT cycle.

Preventing Acute Syndrome Related to Hormone Release. PRRT, in general, is well tolerated and has minimal acute side effects; however, there remains a theoretic risk of acute precipitation of syndrome due to sudden hormone release that would need urgent management: this risk is more likely in patients with large functioning hepatic metastases. Priming this group of patients with cyproheptadine from 1 to 2 d before PRRT may help: we have adopted this practice on a regular basis, and in our experience with close to 500 therapeutic procedures we have not encountered acute syndrome in any of them.

Patients with Poor Nutrition Status. Nutrition status is particularly relevant in developing countries in which the baseline nutrition status of patients is poor. Tryptophan loss, gastrointestinal loss of protein, and liver metastases leading to hepatic dysfunction are other causes of severe hypoalbuminemia, leading to anasarca, abdominal distension, breathlessness, and general deterioration of the patient. In our experience, aggressive oral and intravenous albumin supplementation in this group of patients, along with octreotide therapy before and (if required) after PRRT, increases the number of patients who can undergo PRRT. Increasing intravascular albumin levels improves renal blood flow and reduces the chances of holding back PRRT or its complications. Increased albumin reduces fluid overload and prevents cardiac dysfunction, especially in patients with carcinoid heart syndrome.

Individualized Management. Developing an individualized model is the need of the hour in the management algorithm of NETs, which are a widely heterogeneous group of malignancies with a broad range of tumor differentiation (*2*). A high Mib1 index and avid ^{18}F-FDG uptake are biomarkers of aggressive behavior in NETs, and treatment with chemotherapy or targeted therapy in addition to PRRT may improve the outcome. This, of course, needs examination in a prospective setting.

Dose Fractionation in Neoadjuvant Setting Versus Metastatic Palliation. The usual administered activity of ^{177}Lu-DOTATATE ranges from 5,550 to 7,400 MBq (150–200 mCi) administered at a 10- to 12-wk interval for 4–6 cycles. With some promise of this agent in the neoadjuvant scenario being reported (*3,4*), it needs to be determined whether the same dose fractionation schedule holds well for metastatic palliation as well. It is imperative that in the former setting a more aggressive approach and fewer cycles be used, whereas in a purely palliative setting a fractionated regime incorporating more cycles with smaller doses over a longer period could be useful.

Choice of Medications for Symptomatic Support. A substantial fraction of patients harbors a constellation of symptoms, especially during their initial courses of PRRT. In addition to the short-acting octreotide formulation, they would need symptomatic support for pain relief (tramadol, reasonably safe in mild to moderate renal and hepatic dysfunction, is a good agent for pain management) and for debilitating abdominal spasm (a not infrequent accompaniment in these patients; drotaverine or dicyclomine are useful agents).

Conclusion. The successful delivery of PRRT in patients with NET requires that multiple appropriate supportive measures be considered for symptomatic management. The value of joint dialogue between nuclear medicine physicians and gastrointestinal oncologists for developing an optimal protocol cannot be overemphasized.

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Fatty Acids as a Concept for Probes in Cardiologic PET/MR Imaging

TO THE EDITOR: The June supplemental issue of *The Journal of Nuclear Medicine* reflects and enhances skillful developments in the merging of PET and MR imaging according to the existing status of qualified use. That, in particular, holds for cardiology, as Osman Ratib and René Nkoulou present applications, potential, and the need for PET/MR imaging with the challenging aim of having not just a fusion of two imaging systems but a true synergic benefit (*1*). One masterpiece illustration of the strong and unique power of the PET method in cardiology was a 1999 study by a coeditor of the supplement, Markus Schwaiger, and his group proving the phenomenon of reinnervation in transplanted hearts by use of ^{11}C-hydroxyephidrine and PET (*2*). That is one type of PET application by which PET/MR imaging can open new doors in diagnostic cardiology.

Among various important issues, Osman Ratib and René Nkoulou point out the need for methods to assay myocardial viability, for which PET, indeed, offers substantial possibilities. This need can clearly be understood in the case of coronary artery disease, for which localization and qualification of a stenosis are the first diagnostic steps in a line toward deciding therapeutic strategies to normalize blood flow. Yet, the final question is the effect of coronary artery disease and subsequent therapy on the metabolic situation, as the authors characteristically address with the term *viability,* and possible mismatch between perfusion and metabolism, in general, has to be taken into clinical consideration (*3*).

In that context, we would like to draw attention to the key role of myocardial metabolism in meeting the energy demand of the working heart. This role offers an approach for assaying the viability of the heart muscle. Fatty acids are the main source of energy for metabolism, meeting the instantaneous demand for energy by the myocardium by producing adenosine triphosphate (ATP) as the general fuel for all metabolic reactions and physiologic functions within the organ. In myocardium, ATP is stored in only small amounts, if at all, and therefore has to be formed instantaneously when needed. Within the metabolic turnover, one molecule of palmitic acid results in the formation of 131 molecules of ATP. In the case of glucose, as the second substrate for energy supply, 36 molecules of ATP are formed. Therefore, fatty acids offer the basis for valuable PET probes to assay myocardial viability, and in particular, PET/MR imaging now appears to pave new ways in cardiology by integrating the tracer method using fatty acids labeled with PET radionuclides.

This letter also is being written to recall work with aliphatic and phenyl fatty acids that were radioiodinated and applied in experimental and clinical studies. Both groups of compounds can be prepared with PET radionuclides. ^{11}C-palmitic acid is considered to exhibit some logistic disadvantages; in contrast, 16-^{18}F-palmitic acid is readily obtained by standard radiofluorination protocols and, most interestingly, is known to have a physiologic behavior similar to that of ^{11}C-palmitic acid despite the fluoride substituent (*4*). 15-phenylpentadecanoic acid (PPA) radioiodinated at the benzene ring is efficiently labeled by ^{11}C (*5*). The beneficial aspect of PPA is that β-oxidation results in the release of labeled benzoic acid, which can be used for quantification of the oxidative degradation (*6*). In the past, those structures were modified by various substitutions or insertions into the carbon chain to block or delay metabolic turnover, as blocking was thought to be advantageous just for SPECT imaging (*7*). Radioiodinated PPA was experimentally shown to have a metabolic pathway resembling that of palmitic acid. Most important, among various clinical applications iodophenylpentadecanoic acid was proven to normalize energy metabolism after revascularization (*8*). Furthermore, a modeling approach allows quantification, which may be useful in other therapeutic strategies (*9*). PPA allows direct tracing of both essential metabolic paths: oxidative turnover within β-oxidation and storage in lipids and glycerides.

Because of their general role in energy metabolism, fatty acids do not compete with ^{18}F-FDG as probes for myocardial viability. Although ^{18}F-FDG has a role as a PET probe in cardiology, Osman Ratib and René Nkoulou correctly remind us to the limitations of ^{18}F-FDG as a PET probe.

In summary, fatty acids labeled with PET radionuclides can be considered valuable probes for assay of myocardial viability and may represent a strong tool when PET is merged with cardiologic applications of MR imaging.

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