Clinical Issues Related to Fluid Management during ^{177}Lu-Peptide Receptor Radionuclide Therapy in Metastatic Neuroendocrine Tumors with Carcinoid Heart Disease

We are discussing different clinical issues related to fluid management during the ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in a patient with metastatic neuroendocrine tumors (NET) and carcinoid heart disease. Carcinoid heart disease is an uncommon complication in patients with NET. The incidence of carcinoid tumors is approximately 1 in 75,000 of the population[1] of whom up to 50% develop carcinoid syndrome and it has been noted that once the carcinoid syndrome has developed, approximately 50% of those patients will later develop carcinoid heart disease. Pathogenesis of this syndrome is due to paraneoplastic effects of vasoactive amines released from the tumor, and it manifests commonly as right heart failure due to the involvement of the tricuspid and the pulmonary valves with valvular regurgitation pattern being more common than stenosis.[2] Involvement of left-sided valves can occur though it is less common and seen in patients with patent foramen ovale, high tumor burden, and pulmonary metastasis. The definite management in such patients includes surgical resection/debulking of the primary tumor, symptomatic relief with somatostatin analogs,[3] and surgical approaches for valvular pathology if it is significant. NETs express somatostatin receptor type 2 (SSTR2), which can be targeted using radiopeptides. 90Y-[DOTA] 0-tyr3-octreotide (^{90}Y-DOTATOC) and/or ^{177}Lu-DOTATATE are used for metastatic or inoperable NETs which express SSTR2. One of the limitations of using radiopeptides is that because of their small size; they get filtered through glomerular capillaries in kidney, subsequently reabsorbed and retained in the proximal tubular cells which results in significant radiation absorbed dose to renal tissue.[4] This radiotoxicity is reduced by co-infusion of positively charged amino acids (e g., L-lysine and/or L-arginine) which act by competitively inhibiting the proximal tubular reabsorption of the radiopeptide, hence decrease renal absorbed dose by 9% to 53% as shown by studies.[5] In addition, further reduction in radiation dose can be achieved by further prolonging the amino acid infusion over longer time beyond radionuclide infusion.[4] Apart from amino acid infusion, Gelofusine (a commonly used plasma expander) can be used to further reduce kidney absorbed radiation dose (by about 45%). It acts by blocking the megalin and cubilin receptor-mediated transporter system in proximal tubules.[6] All these methods available to decrease renal absorbed dose are frequently used during PRRT procedure, but all of these require caution in managing patients who have concomitant carcinoid heart involvement. As inadvertent fluid overload can precipitate heart failure in these patients.

The first issue is with the use of Gelofusine, which is a colloid used as a plasma expander. It needs caution to prevent fluid overload as experimental studies have shown that after receiving 1 l of Gelofusine over 1 h, 79% of this volume stays in the intravascular compartment and results in up to 15% rise in intravascular volume.[7] Hence, there is a possibility that it can precipitate heart failure symptoms. Furthermore, one of the side effects is a risk of anaphylaxis with use of gelofuscine.

Other issue while managing these patients is that, while administering the amino acids, they are usually diluted in normal saline to avoid infusing hyperosmotic solution (typical concentration being 25 g amino acid in 1 L of saline). Different regimens have been suggested in guidelines like 1 day 50 g, or 3 days 50 g or 3 days 25 g protocols. However, exact protocols to be used in patients with the carcinoid heart disease are lacking. Though the guidelines suggest joint management of such cases with the cardiologist and taking meticulous care of fluid management.[8] In this regard, 3 days 25 g protocol seems more appropriate as no larger amount of volume is given in short time.

These considerations in patients of carcinoid heart disease are to prevent precipitation of heart failure or prevent worsening of heart failure symptoms.

The management of these patients is complex because both the malignant disease and the cardiac status have to be addressed at the same time. Chronic medical management for right heart failure (i.e., even before the planned PRRT procedure) requires the use of diuretics such as loop diuretics combined with aldosterone receptor antagonists. Diuretics relieve edema and hepatic congestion, but aggressive therapy can result in intravascular depletion and decrease cardiac output. During the PRRT procedure, amino acid infusion and use of gelofusine can increase plasma volume and hence may require additional doses of IV loop diuretics with careful monitoring.[9] Digoxin may be beneficial for these patients with reduced right ventricular contractility.

Another issue during the PRRT procedure is the risk of hypotension due to precipitation of carcinoid crisis. This can occur due to cell killing and release of vasoactive amines. It is a life-threatening condition that can be triggered by tumor manipulation (e.g., biopsy, surgery) or by anesthesia, however, seen less commonly after chemotherapy or radionuclide therapy, that too in patients with extensive tumor burden.[10,11] Since there is the

potential for unpredictable vasoactive amine release which may result in hypotensive crises and hemodynamic collapse, therefore to prevent carcinoid crisis perioperatively during a surgical procedure, IV octreotide infusion is given at a rate of 50–100 mcg/h, starting 12 h preoperatively and is continued throughout the procedure and postoperatively. Carcinoid crisis if occurs during the surgery is managed with octreotide infusion (500–1000 mcg intravenously or a continuous intravenous drip of octreotide at a rate of 50–200 mcg/hour may also be used).[12]

Now for PRRT procedure, the risk of carcinoid crisis increases, because somatostatin analogs are stopped before therapy (4 to 6 weeks for long-acting analogs and at least 24 h for short-acting formulations) because they act on same SSTR and interfere with receptor targeting and efficacy of radionuclide treatment. If carcinoid crisis occurs, it should be readily diagnosed and can be managed in the same lines as managed during the peri-operative period. Experimental studies have shown that the peak serum concentrations of octreotide occur within 30 min after subcutaneous administration and within 4 min after a short (3 min) intravenous infusion and the elimination half-life is approximately 1–5 h.[13,14] Dosimetry and pharmacokinetics study of ^{177}Lu-DOTATATE have suggested that tumor uptake of ^{177}Lu-DOTATATE reaches the peak early at around 3 h postinjection and decreases over time.[15] This suggests that if octreotide injection is used during the situation of carcinoid crisis during the procedure, it probably will decrease the efficacy of therapy, but further studies in this selected population group are suggested.

These scenarios highlight the need to identify patients of NET with carcinoid heart disease because; they require multidisciplinary care even before PRRT and during the procedure to prevent precipitation of heart failure.

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Conflicts of interest

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Saurabh Arora, Averilicia Passah, Nishikant Avinash Damle, Chandrasekhar Bal, Dinkar Bhasin[1], Rajeev Narang[1], Madhav Prasad Yadav, Sanjana Ballal

Departments of Nuclear Medicine and [1]Cardiology, AIIMS, New Delhi, India

Address for correspondence: *Dr. Nishikant Avinash Damle, Department of Nuclear Medicine, AIIMS, Ansari Nagar, New Delhi - 110 029, India. E-mail: nkantdamle@gmail.com*

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