CASE REPORT

Initial clinical experience with indigenously produced [177Lu] Lu-DOTA-TATE in small bowel carcinoid tumor - a case report

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ABSTRACT

Background: Carcinoids are slow-growing neuroendocrine tumors that can be found throughout the gastrointestinal tract and in other organs like the lungs and kidneys. These tumors are capable of metastasis and production of certain chemicals, e.g., serotonin that can cause carcinoid syndrome. Initial treatment is surgery; however, inoperable or metastatic carcinoid tumors can be treated with peptide receptor radionuclide therapy using [^{177}Lu]Lu-DOTA-TATE which can provide symptomatic relief and also slows the disease progression.

Case presentation: We present here a case of gastrointestinal carcinoid in a 65-year-old male patient treated with indigenously produced [^{177}Lu]Lu-DOTA-TATE. The patient presented 3 years after the resection of the intestinal mass and was on somatostatin analogues for control of flushing and diarrhea. Investigations revealed a focal lesion in the liver for which [^{177}Lu]Lu-DOTA-TATE therapy was planned. The patient underwent four cycles of [^{177}Lu]Lu-DOTA-TATE therapy with no undesirable side effects. Six months follow-up investigations after the completion of four cycles of [^{177}Lu]Lu-DOTA-TATE therapy showed no interval progression and a better control of symptoms.

Conclusion: [^{177}Lu]Lu-DOTA-TATE therapy is an effective but expensive treatment for patients having symptomatic disease and inoperable or progressive neuroendocrine tumors; that do not respond well to conventional treatments. Until recently, [^{177}Lu] Lu-DOTA-TATE had to be imported for use in such patients which increased its cost even more. However, the initiative for the production of this radio-pharmaceutical in Pakistan has made it easier to acquire and also lowered the cost significantly.

Key words: PRRT, [^{177}Lu]Lu-DOTA-TATE therapy, neuroendocrine tumors, small bowel carcinoid.

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Background

Neuroendocrine cells are found in organs throughout the body. Carcinoid tumors are usually slow-growing neuroendocrine tumors that can occur in the entire intestine and various other organs of the body. Small intestine carcinoids are the classical carcinoids that can secrete serotonin, tachykinins, etc., which may cause flushing (90 %), diarrhea (70 %), occasional bronchospasm (15%), or carcinoid heart disease. These tumors are rare in children and more common in adults. Neuroendocrine tumors are often diagnosed when the disease has already metastasized or the patient has started experiencing significant symptoms that constitute carcinoid syndrome. Certain biochemical markers, contrast-enhanced computerized tomography (CECT), and somatostatin receptor imaging are used to diagnose the primary site of the tumor and areas involved in its metastasis. Surgery is generally the initial preferred treatment for neuroendocrine tumors; however, due to the indolent nature of the disease, many patients are diagnosed with inoperable, locally advanced, or metastatic disease [1,2].

[^{177}Lu]Lu-DOTA-TATE serves as an effective therapy for patients with advanced somatostatin receptor-positive neuroendocrine tumors, that progress on conventional treatments. Improvements in disease control rates, progression-free survival, overall survival, and quality of life have added this radiopharmaceutical agent to a place of primary consideration in advanced disease management [3]. The recent initiative for the production of [^{177}Lu] Lu-DOTA-TATE in Pakistan has made it possible for us to

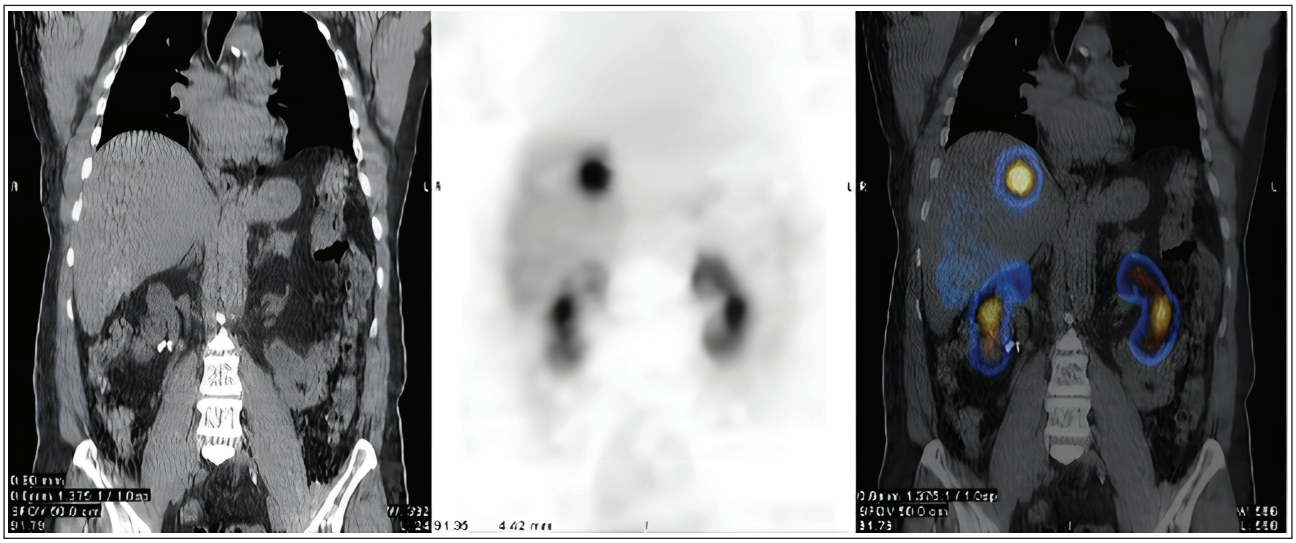

Figure 1. *SPECT CT images of baseline [^{99m}Tc]Tc-HYNIC-TATE scan acquired in July 2023, showing a well-circumscribed solitary focus in segment VII of liver.*

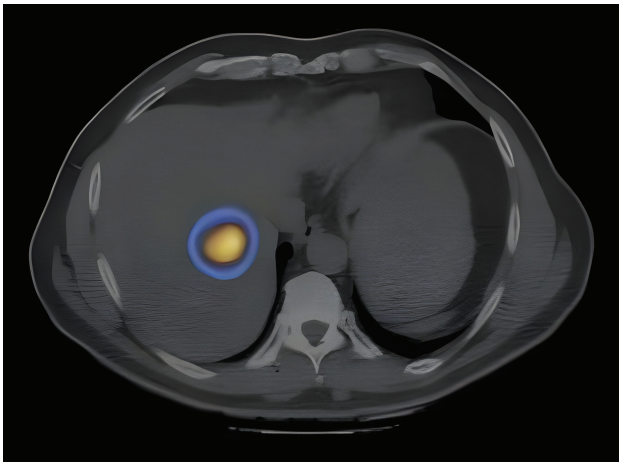

Figure 2. *Post-therapy scan acquired 24 h after injection of a second dose of [^{177}Lu]Lu-DOTA-TATE (7.4 GBq).*

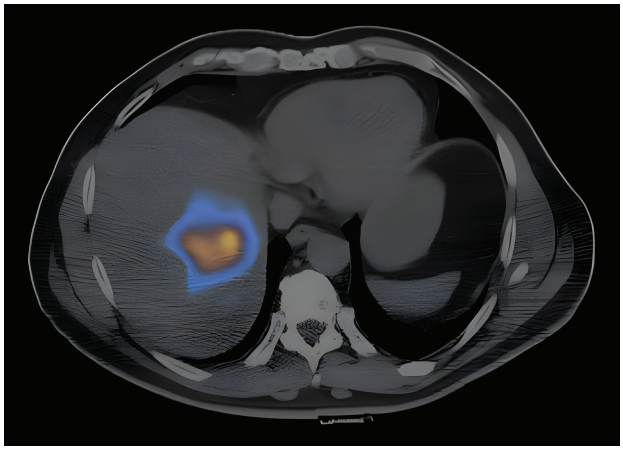

Figure 3. *Post-therapy scan acquired 24 h post-injection of 4th dose of [^{177}Lu]Lu-DOTA-TATE (7.4 GBq).*

share our clinical experience with indigenously produced [^{177}Lu]Lu-DOTA-TATE in small bowel carcinoids.

Case report

A 65-year-old male was diagnosed with Grade 2 small bowel carcinoid on mesenteric lymph node biopsy. Further investigations revealed a small liver lesion and another lesion in the small intestine. The liver lesion was treated with radio-frequency ablation and the small intestine lesion along with mesenteric lymph nodes were excised. Somatostatin analogue therapy was initiated following surgery for the control of significant flushing and severe diarrhea. A CECT 3 years later showed a lesion measuring 35 mm in segment VII of liver. [^{99m}Tc]Tc-HYNIC-TATE scan acquired in July 2023 showed a well-circumscribed radiotracer-avid lesion measuring 35 mm × 34 mm in size in segment VII of liver (Figure 1). Following that the patient was planned for [^{177}Lu]Lu-DOTA-TATE therapy with indigenously produced radio-pharmaceutical.

A total of four doses of [^{177}Lu]Lu-DOTA-TATE (7.4 GBq) were given every 2 months from August 2023 to February 2024. Pre-therapy medication including antiemetics and anti-allergics followed by amino acid infusion containing arginine and lysine were given for the protection of kidneys [3]. Planner whole body post-therapy scans were acquired at 1 h, 4 h, 24 h, and 48 h post-injection of [^{177}Lu]Lu-DOTA-TATE. SPECT/CT images were acquired at 24 h post-injection (Figures 2 and 3). Moreover, SPECT images acquired at 24 h, 48 h, and 7 days post-therapy were used for dosimetry calculations. During all four cycles of [^{177}Lu]Lu-DOTA-TATE therapy, the patient continued short or long-acting somatostatin analogues for control of flushing and severe diarrhea. Investigations including complete blood count, liver function tests, renal function tests, serum electrolytes, and blood glucose levels were checked before each [^{177}Lu] Lu-DOTA-TATE therapy cycle and repeated 1 month later so that he could be closely monitored for signs of bone marrow suppression and changes in renal functions.

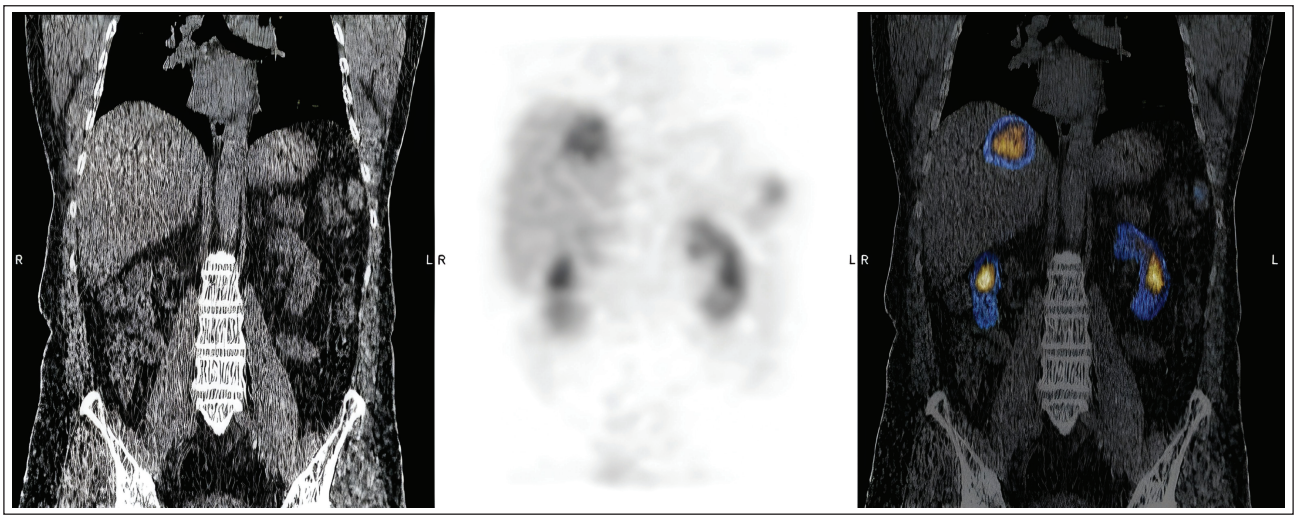

Figure 4. *SPECT CT images of [^{99m}Tc]Tc-HYNIC-TATE scan acquired 6 months after completion of four cycles of [^{177}Lu]Lu-DOTA-TATE therapy in August 2024; showing an irregular shaped lesion with central area of necrosis in segment VII of liver.*

However, no clinically significant change from baseline was observed after completion of standard four cycles, and all levels remained within the normal range.

Six months after completion of [^{177}Lu]Lu-DOTA-TATE therapy, the patient reported improved levels of physical activity, improved appetite, and reduction in flushing and diarrhea. Investigations revealed no significant changes in bone marrow reserves and preservation of renal functions. In comparison with the baseline [^{99m}Tc]Tc-HYNIC-TATE scan of July 2023, the August 2024 [^{99m}Tc]Tc-HYNIC-TATE scan showed no increase in the size of liver lesion in segment VII and measured 35 mm x 33 mm in size (Figure 4). The lesion appeared less intense, had an irregular outline, and showed a central area of reduced radiotracer uptake probably due to necrosis. The lesion to liver percent radiotracer uptake had reduced from 74% to 58%, respectively. Following each [^{177}Lu]Lu-DOTA-TATE PRRT cycle, dosimetry for kidneys and indirect assessment for bone marrow reserves were performed to confirm the safety of the given therapy and also to see if extended therapy with [^{177}Lu]Lu-DOTA-TATE can be administered.

Discussion

Carcinoids are slow-growing neuroendocrine tumors that can occur in the entire intestine and various organs of the body. Some of these tumors are capable of producing certain chemicals, e.g., serotonin, tachykinins, and so on, which can result in flushing, diarrhea, wheezing or bronchospasm, and carcinoid heart disease, leading to the development of carcinoid syndrome. Due to the indolent nature of these tumors, they are often diagnosed late in the course of the disease and sometimes after the development of carcinoid syndrome or metastatic disease, limiting the treatment options. Diagnosis is often carried out by measuring certain biomarkers, CECT, or somatostatin receptor imaging. Surgery is the preferred treatment; however, a curative surgical procedure is often not possible. In such advanced cases, somatostatin analogues and [^{177}Lu]Lu-DOTA-TATE therapy can be helpful in controlling disease-specific symptoms and slow down the disease progression [2,3].

To look at the effectiveness and safety of this treatment we performed simple count-based calculations to see the lesion-to-liver ratios on pre-therapy and post-therapy [^{99m}Tc]Tc-HYNIC-TATE scans. Also, dosimetry calculations after each PRRT cycle were performed to evaluate the cumulative absorbed dose of tumor and kidneys, and indirect assessment of bone marrow reserves; to decide whether further therapy cycles can be administered safely [4]. Kidney dosimetry is a challenging task that has multiple steps and requires sophisticated software and equipment. For our patients, SPECT based method was used that requires multiple post-therapy scans for up to7 days [5]. Imaging and time activity curves for [^{177}Lu]Lu-DOTA-TATE decay showed good retention of the tracer in the liver lesion for up to 7 days. For indirect assessment of kidneys and bone marrow reserves, renal function tests and complete blood counts 1 month after each PRRT cycle were checked and then every 2 months over the next 6 months following completion of therapy.

In our experience, kidney dosimetry and biochemical assessment of renal and bone marrow reserves not only helped to establish the safety profile of indigenously produced [^{177}Lu]Lu-DOTA-TATE but also helped us to consider the possibility of extended dose following standard four cycles of PRRT. The median progression-free survival is although more than 20 months after PRRT, most of the patients may relapse after 2-3 years. Patients with disease progression who have previously responded to standard PRRT cycles and have favorable bone marrow and renal reserves, are suitable candidates for extended cycles of low-dose PRRT [6]. A recent single-center study observed neuroendocrine tumor patients who had received

extended doses of PRRT following disease progression. They found no clinically significant difference between the occurrence of short and long-term hematologic toxicities as well as renal toxicity following standard initial or extended doses of PRRT [7]. Therefore, extended doses or repeat PRRT may benefit selected patients and have an acceptable safety profile.

NETTER-2 trial has proven the efficacy of PRRT in grade 2 and grade 3 well-differentiated neuroendocrine tumors. It has also shown that the use of long-acting somatostatin analogues alongside PRRT significantly improves progression-free survival as compared to high-dose somatostatin analogue therapy alone in neuroendocrine tumor patients. PRRT with [^{177}Lu]Lu-DOTA-TATE plus long-acting somatostatin analogues can be considered the new standard of care in first-line therapy for grade 2 and 3 gastroenteropancreatic neuroendocrine tumors [8,9].

Conclusion

PRRT using [^{177}Lu]Lu-DOTA-TATE is the new standard of care for patients with inoperable or progressive neuroendocrine tumors; that do not respond well to conventional treatments. Due to the indigenous production of [^{177}Lu]Lu-DOTA-TATE, it is now possible to provide this effective treatment to our patients at a significantly lower cost. A careful, planned, and appropriate use of [^{177}Lu]Lu-DOTA-TATE along with long-acting somatostatin analogues has a good safety profile, due to which it can help to significantly improve the quality of life and increase the progression-free survival in patients with symptomatic disease and inoperable or metastatic gastroenteropancreatic neuroendocrine tumors.

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