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CASE REPORT

Lutetium-177 DOTATATE Therapy for Neuroendocrine Tumours: Report of Two Cases

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INTRODUCTION

Neuroendocrine tumours (NETs) are rare but the incidence has been reported to be increasing in recent years.[1] NETs are characterised by their ability to produce and secrete a variety of peptide hormones. The primary treatment modality for NETs is surgical[2] but most patients present with disseminated inoperable disease.[3] Owing to the high-level expression of somatostatin receptors in NETs, especially subtypes 2 and 5, peptide receptor radionuclide therapy (PRRT) with radioactive somatostatin analogues have recently been developed and show promising results.[4] Yttrium SST2 analogues have been used in our hospital for PRRT in the past. Lutetium-177 (Lu-177) has been available in Hong Kong only since 2016. Two patients were referred to our unit between July 2017 and September 2018, and have completed treatment cycles with PRRT. The aims of this report are to summarise and present our treatment results and to assess the clinical safety and potential complications in those patients who received Lu-177 DOTATATE PRRT at our unit.

CASE 1

A 57-year-old man presented in August 2015 with a 3-month history of obstructive jaundice. Investigations revealed a pancreatic head mass with cytology suggestive of NET. Total pancreatectomy was performed in February 2016 with histopathology showing grade 1 NET and one-quarter of the peripancreatic lymph nodes were positive. He was closely monitored. Unfortunately, Ga-68 DOTATATE positron emission tomography/computed tomography in December 2016 showed bilobar hepatic metastases. He was initially started on lanreotide but follow-up imaging confirmed disease progression with abdominal discomfort. He was then referred in May 2017 for PRRT at our unit. Initial chromogranin A (CgA) was 276 ng/mL (normal reference range, 27-94 ng/mL). He received 5 cycles of 150 mCi Lu-177 DOTATATE at 8- to 10-week intervals, with the first cycle given in July 2017. Renal protective amino acids were infused 30 minutes before administration of the radiopharmaceutical. He experienced no immediate adverse effects or hormone-related crisis. Scintigraphy

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Ethics Approval: The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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with single-photon emission computed tomography/computed tomography was performed 4 days after each cycle. Initially there was intense Lu-177 DOTATATE uptake over the hepatic metastases. Subsequently, scintigraphy revealed interval decrease in size and tracer uptake of the lesions. His last treatment cycle was in March 2018 and only minimal uptake was seen in the liver lesions on the final (fifth cycle) post-therapy scan

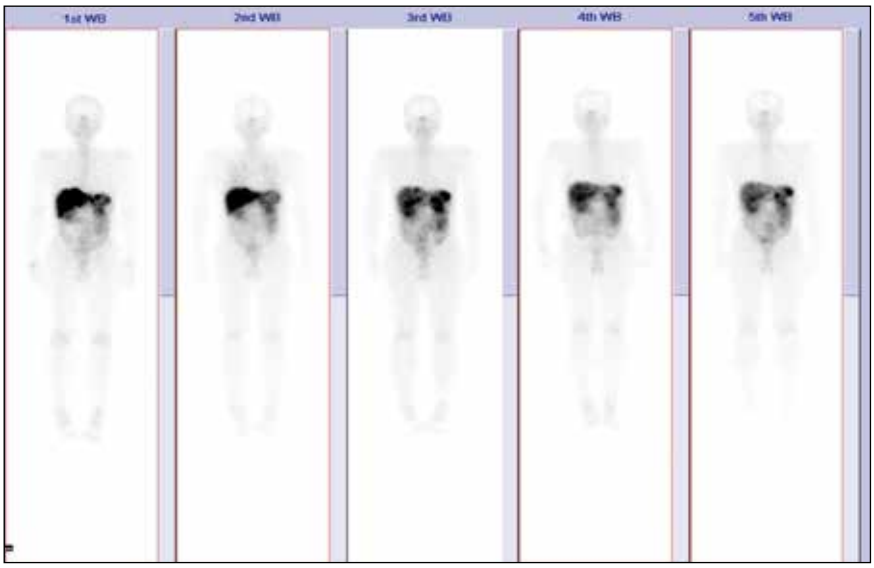

Figure 1. Five treatment cycles were given to this 57-year-old man in 8- to 10-week intervals from July 2017 to March 2018. Serial whole-body planar images from left to right show post-therapy scans. There is an interval decrease in the uptake intensity of the liver lesions.

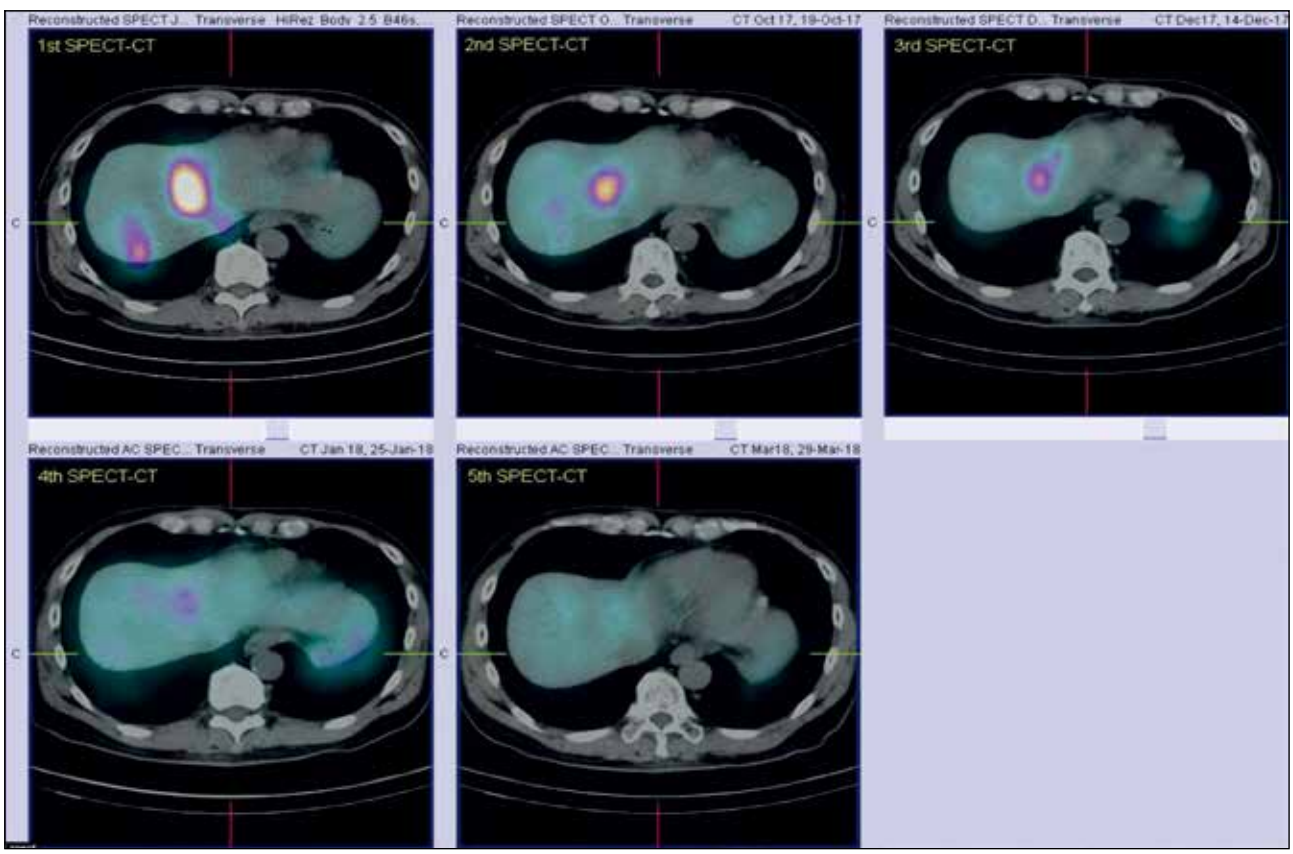

Figure 2. Serial axial single-photon emission computed tomography/computed tomography images in the same 57-year-old man from left upper corner to right lower corner showing an index lesion at the dome of the hepatic lobe at different post-therapy scans. There is an interval decrease in size and uptake intensity of the lesion.

(Figures 1 and 2). Blood test results at 2-week intervals after each cycle for complete blood count, liver and renal function were unremarkable. His symptoms had subsided after the second cycle of treatment. His CgA had reduced to 127 ng/mL at his last follow-up in July 2018 and he was symptom-free.

CASE 2

In May 2015, a 69-year-old woman underwent surgery in China for removal of a rectal NET (medical records are incomplete). Histopathology showed grade 2 NET. An octreotide scan in July 2015 was negative and she was kept under observation. Multiple hepatic metastases were found on computed tomography in February 2016. She was given lanreotide followed by everolimus but subsequent imaging revealed persistent disease progression. She was then referred to our unit for PRRT. The patient's chief complaint was of mild abdominal pain. Octreotide scan in August 2017 showed multiple liver and left common iliac nodal metastases. Her initial CgA was 195 ng/mL. She was treated with 5 cycles of 150 mCi Lu-177 DOTATATE at 8- to 10-week intervals with the first cycle beginning in October 2017. Renal protective amino acid infusion, post-therapy scintigraphy, and follow-up blood tests were similar to those of Case 1. In the first 3 cycles, the patient complained of mild nausea after infusion of the radiopharmaceutical, resolved with antiemetics, but no hormone-related crisis. The first scan after therapy demonstrated intense uptake over the liver, left iliac nodal and right pubic bony metastases. Subsequent scintigraphy showed interval reduction in the nodal lesion size and uptake intensity while the skeletal and hepatic lesions remained relatively unchanged (Figure 3). Her last treatment cycle was in July 2018. Only transient grade 1 marrow toxicity was encountered in the last blood test, otherwise there was no persistent hepatic or renal impairment. The patient's symptoms improved after each treatment cycle. Her CgA had reduced to 22 ng/mL at her last follow-up visit in September 2018.

DISCUSSION

Because of the high-level expression of somatostatin receptors, NETs are ideal neoplasms for treatment with PRRT. Since the publication of the landmark randomised NETTER-1 study in 2017 that showed a markedly longer progression-free survival and significantly higher response rate compared with high-dose long-acting release octreotide among patients with advanced midgut NET, there has been growing interest in the therapeutic application of radio-labelled somatostatin analogue therapy for these patients.[5] Lu-177 has been available in Hong Kong only since 2016. To the best of our knowledge, we are the first public hospital in Hong Kong to provide this treatment. The inclusion and exclusion criteria for PRRT in our institution are

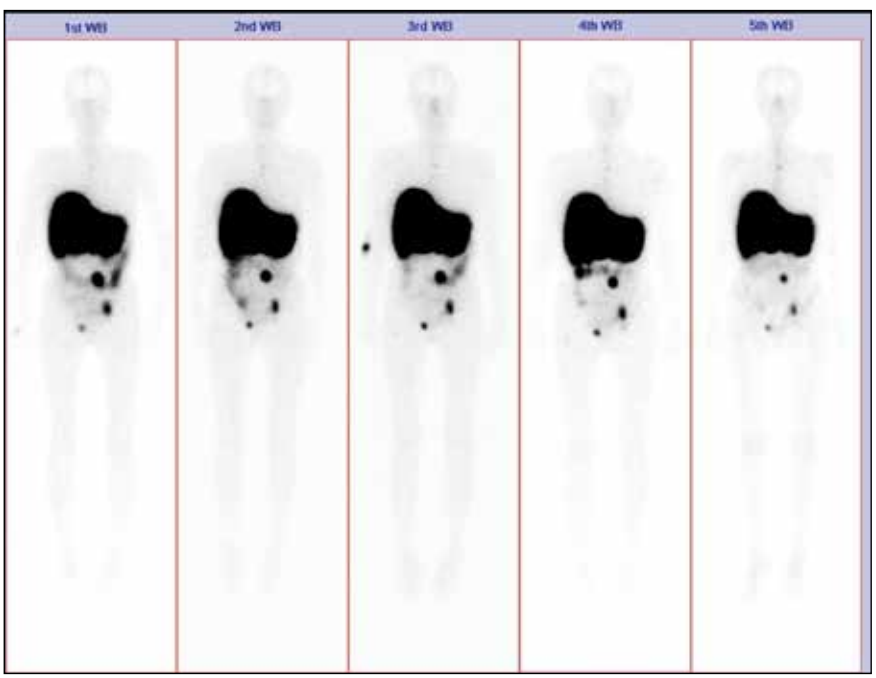

Figure 3. Five treatment cycles were given to this 69-year-old woman in 8- to 10-week intervals from October 2017 to July 2018. Serial whole-body planar images from left to right show post-therapy scans. There is interval decrease in size and uptake intensity for the nodal lesions at the left common and external iliac regions. The hepatic and right pubic skeletal lesions remain grossly similar.

mainly in accordance with recommendations of the joint International Atomic Energy Agency, European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging.[6] Patients referred with inoperable NET and proven somatostatin receptor avidity on scintigraphy without severely compromised bone marrow and renal function, as suggested in the guideline,[6] are considered candidates for such therapy.

A total of 10 cycles of therapy were given to our patients. The most frequent acute adverse effect observed in the first 24 to 48 hours after administration of PRRT was nausea (in 3 out of 10 cycles, 30%) but it was transitory and mild in severity and alleviated by prescription of an antiemetic. Neither patient reported increased abdominal pain or any hormone-related crisis. Our finding of few and mild adverse effects are consistent with reported findings.[7-9] During serial serological monitoring after therapy, in 10 treatment cycles only 1 (10%) instance of transient grade 1 marrow toxicity was encountered. Öberg[8] and Seregni et al[10] reported transient low-grade marrow toxicity in 20% and 23% of patients, respectively. No myelodysplastic syndrome was observed in our patients. This may partly be related to the relative short follow-up period as this serious adverse effect may take up to months or years to develop.[11] There was no hepatic or renal impairment in our patients. In one study by Kwekkeboom,[7] more than half of the patients complained of alopecia. Nonetheless this was not evident in our patients. Overall, the treatment was well tolerated.

Despite being a preliminary study, our results based on scintigraphic findings are quite promising. One of our patients achieved a partial treatment response while the other remains stable according to RECIST criteria. A response rate of 18% was achieved in the Lu-177 DOTATATE treatment groups in the NETTER-1 study.[5] Other studies by Matović,[12] Kwekkeboom et al,[7] and Basu et al[13] reported patient response rates of 26%, 46%, and 60%, respectively. Our observed scintigraphic improvements were slightly superior to those reported in the literature, although our study is preliminary with only two patients. Improved scintigraphic findings in our patients was coupled with improved symptoms and biochemical findings. Both patients demonstrated improvement or resolution of symptoms after treatment. At a biochemical level, our patients presented with elevated tumour marker levels before therapy, and both had an interval decrease in tumour marker level after treatment. Hervás et al[9] evaluated treatment response in seven neuroendocrine patients treated with PRRT, five of whom presented with raised tumour markers before therapy and all demonstrated interval improvement after treatment. Biochemical improvement after treatment was also observed by Basu et al[13] with reduced CgA level in three of five reported cases.

Since NETs are rare and our PRRT service with Lu-177 was started only in 2017, our study is limited to two cases. The preliminary nature of this report also limits evaluation of long-term toxicity and treatment response. Future studies with a larger number of patients and longer follow-up period are needed to enable more in-depth assessment of adverse effects and outcome parameters such as time to progression or overall survival.

CONCLUSION

Our initial experience suggests that PRRT is a safe and effective treatment for metastatic inoperable NETs.

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