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LETTERS

RESEARCH LETTER

Lutetium-177 DOTATATE Therapy and Cardiac Outcomes in Patients With Neuroendocrine Tumor and Cardiac Metastases

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The clinical sequelae of cardiac metastases from neuroendocrine tumors (NETs) are not well defined.[1] Peptide receptor radionucleotide therapy (PRRT), such as lutetium-177 (^{177}Lu) DOTATATE, targets somatostatin receptors on NET cells with cytotoxic β-emission radiation and is an effective treatment for primary NETs.[2] However, ^{177}Lu DOTATATE may have local and systemic inflammatory adverse effects, known as "flare reactions," and its safety in patients with cardiac metastases from NETs is unknown.[3] As such, we sought to evaluate the clinical outcomes of patients receiving ^{177}Lu DOTATATE therapy in this rare cohort.

This study was approved by the Mayo Clinical Institutional Review Board and complied with the Declaration of Helsinki. All patients who underwent ^{68}Ga DOTATATE positron emission tomography for NET across 3 tertiary centers in the United States between 2016 and 2022 were retrospectively reviewed. Of 3,253 patients with primary NETs, 51 patients (1.6%) were identified to have cardiac metastases (stage IV, highly differentiated NETs).

The mean ± SD age was 67.3 ± 11.8 years, and 52.9% were men. Three patients underwent surgical resection of cardiac metastases, and of the remaining 48 patients, 21 (43.8%) received somatostatin analogue (SSA) therapy alone or surveillance, and 27 (56.2%) underwent ^{177}Lu DOTATATE therapy following disease progression on SSA therapy. There were no significant differences in the baseline characteristics, oncological characteristics, or echocardiographic measurements between the 2 treatment groups who did not undergo surgery (**Table 1**).

Over a median follow-up of 3.6 years (Q1-Q3: 1.6-5.6 years) from the identification of cardiac metastases, 12 patients (23.5%) died. Ten died because of progression of underlying malignancy and 2 died in the community (outside of our institution's care) with unknown causes of death. Through 5 years following the identification of cardiac metastases, there was not a statistically significant difference in the mortality rate between those receiving ^{177}Lu DOTATATE treatment and those receiving SSA or surveillance therapy (log-rank $P = 0.47$), with 5-year Kaplan-Meier mortality estimates of 22.4% and 14.8%, respectively. This finding remained unchanged using a Cox regression analysis considering commencement time of ^{177}Lu DOTATATE therapy as a time-dependent

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Demographics and Tumor Characteristics for Whole Patient Cohort and Separated by Treatment Modality

	All Patients (N = 51)	Surgical Resection[a] (n = 3)	Somatostatin Analogue/Surveillance[b] (n = 21)	^{177}Lu DOTATATE Therapy (n = 27)	*P* Value[c]
Comorbidities					
Age at detection of cardiac metastases, y	67.3 ± 11.8	51.8 ± 12.1	66.3 ± 11.6	68.8 ± 11.9	0.47
Male	27 (52.9)	2 (66.7)	11 (52.4)	15 (55.6)	0.83
Hypertension	12 (23.5)	1 (33.3)	4 (19.0)	8 (29.6)	0.40
Diabetes	4 (7.8)	1 (33.3)	0 (0.0)	4 (14.8)	0.12
Atrial fibrillation	2 (3.9)	1 (33.3)	0 (0.0)	1 (3.7)	0.40
Coronary artery disease	3 (5.9)	0 (0.0)	2 (9.5)	1 (3.7)	0.41
Primary tumor location					0.19
Small bowel	25 (49.0)	1 (33.3)	9 (42.9)	15 (55.6)	
Pancreas	8 (15.7)	0 (0.0)	4 (19.0)	4 (14.8)	
Large bowel	4 (7.8)	1 (33.3)	2 (9.5)	1 (3.7)	
Other	4 (7.8)	1 (33.3)	0 (0.0)	3 (11.1)	
Unknown	10 (19.6)	0 (0.0)	6 (28.6)	4 (14.8)	
Cardiac metastases location					0.64
Left ventricle	23 (45.1)	0 (0.0)	11 (52.4)	12 (44.4)	
Right ventricle	9 (17.6)	1 (33.3)	4 (19.0)	4 (14.8)	
Interventricular septum	4 (7.8)	0 (0.0)	1 (4.8)	3 (11.1)	
Pericardial	8 (15.7)	0 (0.0)	2 (9.5)	6 (22.2)	
Atria	7 (13.7)	2 (66.7)	3 (14.3)	2 (7.4)	
Mass seen on transthoracic echocardiography	5 (9.8)	2 (66.7)	3 (14.3)	0 (0.0)	0.07
Time from diagnosis of NET to detection of cardiac metastases, y	5.6 (0.9-9.8)	0.1 (0.1-3.5)	3.5 (0.1-9.8)	6.4 (2.0-9.8)	0.31
Krenning score					0.18
3	10 (19.6)	0 (0.0)	6 (31.6)	4 (14.8)	
4	39 (76.4)	3 (100.0)	13 (68.4)	23 (85.2)	
Ki-76, %	5.0 (2.4-12.6)	1.0 (1.0-1.0)	5.0 (2.3-12.5)	5.5 (3.0-13.4)	0.82

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Two of the three patients who had surgical resection also received ^{177}Lu DOTATATE therapy and are not included in the ^{177}Lu group. [b]Of the 21 patients in the somatostatin analogue therapy or surveillance group, 19 (90.5%) had treatment with somatostatin analogues. Two (9.5%) did not receive any NET-directed therapy (managed by observation). [c]*P* values represent statistical comparison between the somatostatin analogue therapy or surveillance group and the ^{177}Lu DOTATATE therapy group. Comparisons use Student's *t* test or the Wilcoxon rank sum test for continuous variables and the chi-square or Fisher exact test for categorical variables. The table does not include any statistical analysis of surgical resection group.

NET = neuroendocrine tumor.

covariate. The likelihood of death was higher in the ^{177}Lu DOTATATE therapy group, but the difference was not statistically significant (HR: 3.96; 95% CI: 0.97-16.13; $P = 0.060$).

In the overall cohort of patients with NETs and cardiac metastases without surgical intervention, cardiovascular complications were uncommon. Two patients had heart failure with preserved ejection fraction, 2 had new onset of atrial fibrillation, 3 had low-grade conduction disorders (defined as first- or second-grade heart block), 2 had evidence of carcinoid heart disease, and none had significant arrhythmia (defined as high-grade atrioventricular block or ventricular arrhythmia). There was not a statistically significant difference in the cardiac event rate between patients who received ^{177}Lu DOTATATE therapy and those who received SSA therapy or surveillance (log-rank $P = 0.16$), with a 5-year cumulative incidence of 29.7% and 10.1%, respectively.

This finding also remained unchanged considering the commencement time of ^{177}Lu DOTATATE therapy as a time-dependent covariate. The likelihood of having a cardiac event was higher in the ^{177}Lu DOTATATE therapy group, but this difference was not statistically significant (HR: 3.47; 95% CI: 0.82-14.63; $P = 0.090$). Specifically, patients in the ^{177}Lu DOTATATE therapy group had no episodes of ventricular tachycardia, high-grade conduction disease, pericarditis, or cardiac tamponade (which are specific cardiac events that are typically associated with any cardiac inflammatory or "flare" reaction).

This study, in the largest cohort of patients with NETs with cardiac metastases to date, holds clinical importance, with increasing evidence for the use of PRRT not only as second-line therapy but also more recently as first-line therapy in specific NET subtypes.[4] Furthermore, in addition to improved therapeutic response and prognosis, PRRT has been shown

to result in improved quality of life for patients with NETs.[2,5] There have been theoretical concerns for proinflammatory "flare reactions" from ^{177}Lu DOTATATE therapy, as it shrinks metastatic tumor size with necrosis, which in cardiac tissue may cause myocardial edema, and potential adverse clinical events such as significant arrhythmia (ventricular tachycardia or high-grade conduction disease), heart failure, cardiac wall rupture pericarditis, and tamponade.

There was no significant difference in cardiovascular outcomes, including ventricular systolic function or incidence of new heart failure, conduction disease or arrhythmia, concomitant carcinoid heart disease, pericarditis, and tamponade, between patients with NET cardiac metastases receiving ^{177}Lu DOTATATE therapy and those in the SSA therapy or surveillance group. Overall, these retrospective data suggest that the use of ^{177}Lu DOTATATE therapy in patients with NET metastases was not associated with any significant increase in adverse cardiac events or mortality.

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