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Lanreotide depot (LAN) post-octreotide long-acting release (OCT) for safe and tolerable treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

M Wasif Saif, Julie Fu, Melissa H Smith, Antonia Maloney, Valerie Relias, Barbara J Weinstein, Yvelisse Suarez, Martin D Goodman, Kevin P Daly

Tufts University Medical Center, Department of Hematology/Oncology, Boston, MA, USA

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School of Medicine

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INTRODUCTION

- The incidence of neuroendocrine tumors (NETs) has been increasing rapidly in the US, with Surveillance, Epidemiology, and End Results Program (SEER) data showing a 5-fold increase from 1973 to 2004 (1.09/100,000 to 5.25/100,000)[1,2]
- SEER data also show that the mean overall NETs 5-year survival rate in the US is 68.1% and median overall survival duration is 75 months[1-3]
- Lanreotide depot (LAN) is used for treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in order to improve progression-free survival[4]
- The randomized, double-blind, placebo-controlled Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) trial compared LAN with placebo and demonstrated a significantly prolonged progression-free survival (median not reached vs median of 18.0 months, $P<0.001$; hazard ratio for progression/death for LAN vs placebo, 0.47; 95% CI: 0.30-0.73). At 24 months the estimated rates of progression-free survival were 65.1% (95% CI: 54.0-74.1) vs 33.0% (95% CI: 23.0-43.3) for the LAN and placebo groups, respectively[5]
- Although primary treatment for metastatic NETs often includes somatostatin analogs (SSAs)[2], the tolerability of sequential use of SSAs for GEP-NETs, including octreotide (OCT) followed by LAN, has not been studied in depth

OBJECTIVE

- During this ongoing institutional case series, we assessed the safety and tolerability of LAN in patients with various GEP-NETs who experienced disease progression or lack of tolerance to OCT

METHODS

- Following Institutional Review Board (IRB) approval, a retrospective chart review at Tufts University Medical Center was conducted for NET patients who received LAN post-OCT
- Information obtained included demographic data, tumor stage/grade, SSA treatment/dose, baseline/current levels of biochemical markers (chromogranin [CgA], urinary 5-hydroxyindoleacetic acid [5-HIAA; primary metabolite of serotonin]), radiologic response, and adverse events (AEs)
  - Serological tumor markers were evaluated at each visit
  - 5-HIAA in 24-hour urine were collected every 3-6 months
  - Radiological imaging, including CT scan of abdomen, pelvis, and chest, was performed every 3 months
  - Patients who underwent liver-directed therapy also had a dedicated MRI within 8-12 weeks from the procedure
  - Octreotide scan was performed at baseline and then 6-12 months later to further confirm disease progression or response
- Data for efficacy outcomes such as progression-free survival and overall survival were not available at the time of data collection

RESULTS

- 16 patients (11 female) with nonfunctional and low-grade cecal or pancreatic NETs were included (age range 43-81 years; mean 64.25 years) (**Table 1**)
- Locations of primary tumors and metastatic sites, along with grade, stage, histology, and whether or not they were functional are presented in **Table 1**

Table 1. Baseline and demographic information (N=16)

Patient	Gender, Age (years)	Primary Tumor Location	Metastatic Site(s)	Grade	Stage 1-4	Histology[a]	Mitotic Index (10 HPF)	Ki-67 (%)	Functional/ Nonfunctional
1	M, 81	Duodenum	Liver, mesentery	G1	IV	• Well-differentiated NET	<2	3%	NF
2	F, 68	Antrum	N/A	G1	III	• Well-differentiated NET	<2	5%	NF
3	M, 69	Ileocecum	Right inguinal LN, liver	G2	IV	• Moderately-differentiated, intermediate grade NET	8-10	3%-4%	NF
4	M, 81	Unknown (mesenteric mass)	Abdominal LN	G1	III	• Well-differentiated NET	<2	7%	NF
5	F, 72	Ileum	LN, liver	G2	IV	• Well to moderately-differentiated NET	10	<10%	NF
6	F, 56	Unknown	Liver	G1	IV	• Well-differentiated NET	6-8	8%	NF
7	F, 75	Unknown (mediastinal LN)	Hilar LN	G2	IV	• Moderately-differentiated NET, positive immunohistochemical stains for synaptophysin, chromogranin-A, serotonin and negative for TTF-1, CK7, VIP, S-100, CK20, CDX2, CK5/6, p63, napsin-A	14-15	26%	NF
8	M, 78	Pancreas	Liver, spleen	G2	IV	• Moderately-differentiated NET	5-6	15%	NF
9	F, 60	Ileocecal	Liver	G2	IV	• Moderately-differentiated NET	8	16%	NF
10	F, 53	Pancreas	Liver	G1	IV	• ACTH-producing pancreatic NET complicated by Cushing's syndrome	8	NA	NF
11	F, 64	Gastric	Liver, spleen, bone, lung	G2	IV	• Moderately-differentiated NET	4	10%	NF
12	F, 61	Pancreas	Peritoneum	G1	IV	• Well-differentiated NET	1	NA	NF
13	M, 47	Ileum	Liver, colon	G1-G2	IV	• Well to moderately-differentiated NET	12	16%	NF
14	F, 43	Gastric	Liver	G2	IV	• Moderately-differentiated NET	3	3%	NF
15	F, 56	Pancreas	Liver, LN	G1-G2	IV	• Well to moderately-differentiated NET	6	13%	NF
16	F, 64	Appendix	Peritoneum, LN	G2	IV	• Moderately-differentiated NET	<2	4%	NF

ACTH, adrenocorticotropic hormone; G, grade; LN, lymph nodes; N/A, not assessed; NET, neuroendocrine tumor; NF, nonfunctional.
[a]Poor, moderate, well-differentiated.

- 16 patients receiving OCT 30-60 mg were switched to LAN due to progressive disease (n=3), poor tolerance (n=1), injection discomfort or pain (n=6), or their decision (n=6) (**Table 2**)
- LAN starting doses were 120 mg (n=13), 90 mg (n=1), or 60 mg (n=2) every 28 days based on renal dysfunction
- Median number of LAN doses was 5.25 (range 2-10)
  - All but 1 patient is still receiving LAN
- AEs that occurred among patients after the initiation of LAN are presented in **Table 2**

Table 2. Octreotide to lanreotide depot: reason for switching, dosing, and tolerability (N=16)

Patient	Last OCT Dose (mg)	Reason for Switching to LAN	LAN Starting/ Current Dose (mg)	Total LAN Doses	Adverse Events
1	30 IM	Patient decision	120	9	G1 fatigue
2	30 IM	Patient decision	120	5	None
3	30 IM	Patient decision	120	8	None
4	30 IM	Patient decision	60*	8	None
5	30->40 IM	Increased serologic marker + new liver lesion	120	8	None
6	30 IM	Patient decision	120	3[a]	None
7	40 IM	Diarrhea and abdominal pain	120	2[b] stopped	G1 tremor, G2 hyperglycemia, G1 fatigue, G2 nausea, G1 blurred vision
8	30->40 IM	PD (liver)	120	3	G1 nausea, G1 abdominal pain
9	20 IM	Cost, GI pain, nausea?	120	10	None
10	20 IM	Radiologic and serologic PD	90*	5	None
11	30->60 IM	GI upset, bone progression (stable liver)	120	3	None
12	40 IM	Serologic marker	120	3	None
13	20->40 IM	Patient decision	120	5	G1 diarrhea
14	30 IM	Intolerance, low muscle mass (anorexia)	120	3	None
15	Unknown	Serologic progression	120	3	G1 fatigue
16	30 IM	Buttock pain	60*	6	G1 constipation

CgA, chromogranin; G, grade; IM, intramuscular; LAN, lanreotide depot/autogel; OCT, octreotide; PD, progressive disease.
*Patients #4 and #10 were successfully escalated to full dose without any adverse effects. Patient #16 had dose escalated to 90 mg but not beyond as his kidney function remained to be moderately impaired due to diabetic nephropathy.
[a]Past intolerance to octreotide-associated diarrhea.
[b]Received 1 dose at Roswell; patient received unknown number of additional doses administrated by a healthcare professional closer to the patient's residence.

- All but 1 of the 16 patients had decreases in CgA level after initiation of treatment with LAN (CgA levels: 7-2555 to <5-440 nmol/L) (**Table 3**)
- 5-HIAA values were available for 7 patients (baseline: 3.3-23 mg/L, after treatment: 3.1-16 mg/L)
- Serum serotonin (<10-1290 to <10-533 ng/mL) decreased after initiating LAN
- Concomitant therapies included none (n=8), chemotherapy (n=3), radiofrequency ablation (n=3), and surgery (n=2)
- Radiologic responses were stable disease (n=9), partial response (n=5), progressive disease (n=1), or complete response (n=1)
- Additional serologic markers decreased, including gastrin (n=2; 239 to 76 pg/mL, <100 pg/mL; normal: ≤100 pg/mL), pancreatic polypeptide (n=2; 1221 to 430 pg/mL; normal: 60-69 y: <312 pg/mL), and adrenocorticotropic hormone (n=1; 66 to 10 pg/mL; normal: 6-50 pg/mL) (**Table 3**)

Table 3. Levels of CgA, 5-HIAA, and 5-HT (N=16)

Patient		CgA Level (target 0-5.0 nmol/L)	5-HIAA (target 0-14.9 mg/L)	5-HT (target 21.0-321.0 ng/mL)	Required Concurrent Treatments	Radiologic Response	Other Serologic Markers
1	At initiation of LAN	30	N/A	76	None	SD	Gastrin level reduced (<100 pg/mL)
	Current	39	N/A	79			
2	At initiation of LAN	43	N/A	N/A	None	SD	Gastrin level reduced (239 to 76 pg/mL)
	Current	15	N/A	N/A			
3	At initiation of LAN	7	N/A	373	RFA	PR	None
	Current	<5	N/A	266			
4	At initiation of LAN	224	N/A	432	None	SD	None
	Current	112	N/A	103			
5	At initiation of LAN	18	4.8	686	Y^{90} TARE	PR	None
	Current	14	3.6	533			
6	At initiation of LAN	366	5.7	89	None	SD	None
	Current	224	3.9	71			
7	At initiation of LAN	168	N/A	<10	None	SD	None
	Current	122	N/A	<10			
8	At initiation of LAN	2555	N/A	698	CAPTEM and Y^{90}	PR	None
	Current	204	N/A	89			
9	At initiation of LAN	172	N/A	56	Debulking surgery	SD	None
	Current	29	N/A	76			
10	At initiation of LAN	30	N/A	205	None	SD	ACTH-producing tumor normalized; PPP ↓60% (1221 to 610 pg/mL)
	Current	<5	N/A	201			
11	At initiation of LAN	382	8.7	797	CAPTEM; sunitinib	PD	None
	Current	160	3.1	345			
12	At initiation of LAN	67	N/A	177	5-FU, bevacizumab; debulking surgery	CR	PPP reduced by >50% (1100 to 430 pg/mL)
	Current	>5	N/A	152			
13	At initiation of LAN	93	6.9	1290	RFA	PR	None
	Current	>5	4.1	205			
14	At initiation of LAN	21	3.3	641	RFA	PR	G1 nausea
	Current	18	12.8	29			
15	At initiation of LAN	735	23	56	None	SD	None
	Current	440	16	33			
16	At initiation of LAN	382	10.2	236	None	SD	None
	Current	79	5.5	6.8			

5-HIAA, 5-hydroxyindoleacetic acid; 5-FU, 5-fluorouracil; 5-HT, serotonin; ACTH, adrenocorticotropic hormone; CAPTEM, capecitabine + temozolomide; CgA, chromogranin; CR, complete response; G1, grade 1; LAN, lanreotide depot; N/A, not assessed; PD, progressive disease; PPP, pancreatic polypeptide; PR, partial response; RFA, radiofrequency ablation; SD, stable disease; TARE, transarterial radioembolization; Y^{90}, yttrium-90.

CONCLUSIONS

- LAN was well tolerated among these patients with GEP-NETs who experienced disease progression or lack of tolerance while receiving OCT
- In transitioning from OCT to LAN, levels of CgA decreased in all but 1 of the patients, with the greatest reductions occurring among those who had the greatest levels prior to treatment with LAN
- The prescribing information of LAN includes renal dose adjustments:
  - Moderate to severe renal impairment: initial dose is 60 mg by deep subcutaneous injection every 4 weeks for 3 months, followed by dose adjustments as described for non-renal-impaired patients
- The results presented here indicate safety of LAN among patients with renal dysfunction (n=3), along with safe escalation to the recommended dose
- The results also revealed that combined treatment was safe and effective in patients with NET who underwent liver-directed therapies, including radiofrequency ablation, transarterial radioembolization, and others in combination with LAN
- This case series also revealed radiologic response of LAN in GEP-NETs with 94% of patients responding to LAN (15 of 16 patients, CR n=1, PR n=5, SD=9) and overall serological marker reduction in almost all patients
- Additional studies would help define efficacy and safety in patients who were previously treated with OCT or another SSA
- Saif, et al are currently conducting a retrospective medical chart review that is designed to include data from ~100 patients. The objectives of that review include:
  - Evaluating the efficacy and safety of LAN in a real-world setting
  - Providing additional information on LAN efficacy and safety following treatment with OCT
  - Assessing quality of life and patient satisfaction
  - Reporting the reasons patients were switched from OCT to LAN

REFERENCES

1. Yao JC, et al. *J Clin Oncol.* 2008;26:3063-72.
2. Saif MW. *Expert Opin Pharmacother.* 2016;17:443-56.
3. Lawrence B, et al. *Endocrinol Metab Clin North Am.* 2011;40:1-18, vii.
4. US Food and Drug Administration. Lanreotide. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm427065.htm. Accessed September 19, 2016.
5. Caplin ME, et al. *N Engl J Med.* 2014;371:224-33.

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