Systematic Literature Review of Octreotide's Antitumor Effects in Neuroendocrine Tumors

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Background

- Neuroendocrine tumors (NETs) are rare, slow-growing neoplasms (Broder et al., 2015) that most commonly arise in the gastrointestinal tract, lung, and pancreas (Sidéris et al., 2012).
- Dasari et al. (2017) reported an increase in the annual age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2012 (6.98/100,000).
- For nearly three decades, octreotide (Sandostatin; Novartis) has been a mainstay of metastatic NET treatment. Somatostatin analogs (SSAs), including octreotide, have been recommended by National Comprehensive Cancer Network (NCCN) guideline as the first-line treatment for advanced NETs (NCCN, 2017). However, octreotide is approved in the United States only for carcinoid symptom control, not tumor control.
- Three previous systematic literature reviews have identified studies that assessed octreotide's antitumor effects (Broder et al., 2015; Sidéris et al., 2012; Chan et al., 2017). Broder et al. (2015) and Chan et al. (2017) focused their reviews on SSA escalated dose; Sideris et al. (2012) reviewed the literature pertaining to clinical trials of the antitumor effect of SSAs.
- Limited information is known on octreotide's antitumor effect assessed in real-world retrospective studies in this area.

Objective

- This literature review intends to provide a comprehensive review of the existing evidence on the antitumor effect of long-acting octreotide in NETs regardless of dosing and broadens the search to include both real-world evidence and clinical trials.

Methods

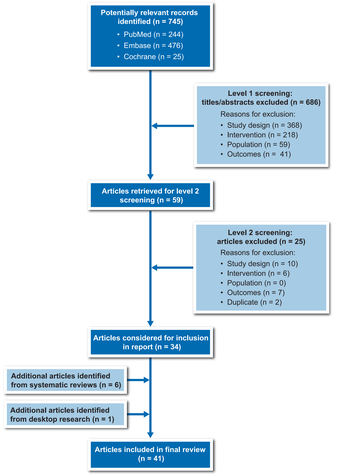
- A systematic literature review of both clinical trials and observational studies was conducted in PubMed, Embase, and Cochrane through January 18, 2017.
- Conference abstracts for 2015 and 2016 from five scientific meetings also were searched:
  - American Society of Clinical Oncology (ASCO)
  - European Society for Medical Oncology (ESMO)
  - North American Neuroendocrine Tumor Society (NANETs)
  - European Neuroendocrine Tumor Society (ENETS)
  - ASCO-Gastrointestinal Cancers Symposium (ASCO-GI)
- Examples of search terms included:
  - Disease- and treatment-specific terms, such as "neuroendocrine tumors," "neuroendocrine neoplasms," "neuroendocrine malignanc*," "neuroendocrine carcinoma," "carcinoid," "octreotide," and "Sandostatin"
  - Various terms to identify specific antitumor and antiproliferative effect and other outcomes of interest, such as "antitumor*," "antiproliferati*," "tumor grow*," "objective response rate," "complete response," "partial response," "stable disease rate," "progression rate," "duration of response," "surviv*," "progression-free survival," "time to tumor progression," "overall survival," "tumor response," "tumor progression," "disease control rate," "progressive tumor," and "anticancer"
  - Terms to identify observational studies, randomized controlled trials, clinical trials, and case series studies, such as "clinical trial," "observational stud*," "systematic literature review," "retrospective studies," "multicenter study," "prospective studies," "clinical trial*," "registries," and "population-based study"
- Two independent reviewers screened the titles and abstracts according to predefined inclusion and exclusion criteria. The inclusion and exclusion criteria are available upon request.

Results

Literature Search Results

- The literature database search identified 745 unique records. Six additional articles were identified following a review of the bibliographic reference lists of relevant systematic review articles. One additional abstract was identified from the search of professional societies and associated conferences.
- A total of 41 publications met inclusion criteria (Figure 1). Of the 41 publications, 20 reported comparative analyses, and 21 reported single-arm studies.

Figure 1. PRISMA Diagram



Overall Study Designs

- Table 1 summarizes the types of studies identified in the literature review.

Table 1. Study Designs of Articles Identified in the Literature Review

Study Designs	Number of Articles
Comparative studies	20[a]
Comparative studies of octreotide versus placebo or no treatment	4
Comparative studies comparing different dosing regimens	5
Comparative studies assessing long-acting octreotide monotherapy versus another monotherapy treatment	3
Comparative studies assessing octreotide combination therapy to octreotide monotherapy	8
Single-arm studies	21
Total	**41**

[a] 12 unique studies, of which 2 were clinical trials and 10 were observational studies.

Key Comparative Study: PROMID (Table 2)

- The phase 3 PROMID clinical trial showed that long-acting octreotide significantly prolonged time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.20-0.59) (Rinke et al., 2009).
- No statistically significant difference in overall survival was observed (Rinke et al., 2017). Note that 33 of the 43 patients randomized to placebo at study entry transitioned to long-acting octreotide after tumor progression (Rinke et al., 2009); this likely confounded the effect of long-acting octreotide on OS (Rinke et al., 2017).

Key Retrospective Studies (Table 3)

- Two multivariable-adjusted, long-term retrospective analyses of overlapping periods of SEER-Medicare data found that long-acting octreotide treatment was associated with longer OS than no long-acting octreotide treatment among patients 65 years or older with distant disease (HR, 0.61; 95% CI, 0.47-0.93 in patients with carcinoid syndrome; and HR, 0.68; 95% CI 0.55-0.84 for NET patients regardless of the presence of carcinoid syndrome) (Shen et al., 2014; Shen et al., 2015).
- Another long-term retrospective study of SEER-Medicare data found that ≤ 20 mg long-acting octreotide was associated with significantly worse OS than 21-30 mg (HR, 2.00; 95% CI, 1.32-3.04) but that ≥ 30 mg was not associated with significantly better OS (Shen et al., 2016).

Additional Studies

- Table 4 presents additional evidence of antitumor effects of octreotide in the other 37 identified studies.

Table 2. Antitumor Effects of Octreotide in the PROMID Trial

Note: Blue shading denotes randomized controlled trials.

	Citation	N	Tumor Type	Treatment and Dose	Study Period and Follow-up	TTP[a]	SD[b]	PR[b]	OS[b]
PROMID	Rinke et al., 2009	85	Well differentiated, advanced NET with midgut or unknown origin, Functional and nonfunctional	Long-acting OCT 30 mg every 28 days (n = 42) vs. PBO (n = 43)	Patients enrolled between March 2001 and January 2008; followed until June 2008	Median TTP OCT: 14.3 mos vs. PBO: 6.0 mos HR: 0.34; 95% CI, 0.20-0.59; *P* = 0.000072	At 6 mos: OCT: 66.7% vs. PBO: 37.2% (*P* = 0.0079)	At 6 mos: 1 in each group	Interim analysis: Median OS OCT: Not reached (> 77.4 mos) vs. PBO: 73.7 mos HR, 0.81; 95% CI, 0.30-2.18; *P* = 0.77
	Rinke et al., 2017	85	Well differentiated, advanced NET with midgut or unknown origin, Functional and nonfunctional	Long-acting OCT 30 mg every 28 days (n = 42) vs. PBO (n = 43)	Patients enrolled between March 2001 and January 2008; followed until May 2014				Final analysis: Median OS OCT: 84.7 mos vs. PBO: 83.7 mos HR, 0.83; 95% CI, 0.47-1.46; *P* = 0.51

mos = months; OCT = octreotide; OS = overall survival; PBO = placebo; PR = partial response; SD = stable disease; TTP = time to progression.

[a] Primary endpoint.

[b] Secondary endpoint.

Table 3. Antitumor Effects of Octreotide in Key Retrospective Studies

Note: Green shading denotes real-world studies.

Citation	N	Tumor Type	Treatment and Dose	Cohort Entry and Follow-up Periods	5-Year Survival	OS
Shen et al. (2014)[a]	1,291	Distant and local/regional disease; well, moderately, and unknown differentiated tumors Functional NETs: 100%	Long-acting OCT (dose not defined) vs. patients who did not receive OCT	**Cohort entry:** July 1999-Dec. 2007 **Follow-up:** through Dec. 2009	**Distant-stage:** HR, 0.61; 95% CI, 0.47-0.79; *P* < 0.001 **Local/regional stage:** HR, 0.88; 95% CI, 0.57-1.36; *P* = 0.563	**Distant stage:** OCT: 2.11 years vs. no OCT: 1.25 years; *P* = 0.002 **Local/regional stage:** "no significant survival benefit"
Shen et al. (2015)[b]	6,940	Distant and local/regional disease; well, moderately, and unknown differentiated tumors Functional and nonfunctional NETs	Long-acting OCT and no long-acting OCT distant stage (n = 1,176) Long-acting OCT and no long-acting OCT local/regional stage (n = 5,764)	**Cohort entry:** Jan. 1999-Dec. 2009 **Follow-up:** through Dec. 2011	—	**Distant stage:** OCT: 35.22 mos vs. no OCT: 19.15 mos HR, 0.68; 95% CI, 0.554-0.840; *P* < 0.001 **Local/regional stage:** OCT: 64.85 mos vs. no OCT: 104.97 mos HR, 1.253; 95% CI, 0.928-1.692; *P* = 0.1415
Shen et al. (2016)[b]	222	Tumor pathology: well, moderately, or poorly differentiated Functional and nonfunctional distant-stage NETs	Long-acting OCT every 28 days by dose: ≤ 20 mg (n = 81) 21-30 mg (n = 82) > 30 mg (n = 59)	**Cohort entry:** Jan. 1999-Dec. 2009 **Follow-up:** through Dec. 2011	—	≤ 20 mg: 20.8 mos 21-30 mg: 32.6 mos > 30 mg: 36.3 mos ≤ 20 mg vs. 21-30 mg: HR, 2.000; 95% CI, 1.318–3.035; *P* = 0.0011 > 30 mg vs. 21-30 mg: HR, 1.094; 95% CI, 0.671–1.7884; *P* = 0.7193

[a] Sample restricted to patients who either never received treatment with long-acting octreotide or who received it within 6 months of the index date.

[b] Sample restricted to patients who either never received treatment with long-acting octreotide or who received it within 12 months of the index date.

Table 4. Antitumor Effects of Octreotide

Note: Blue shading denotes randomized controlled trials; yellow shading denotes controlled trials; green shading denotes real-world studies.

	Citation	N	Treatment	PR	SD	PFS	OS
Different octreotide dosing regimens							
	Ferolla et al. (2012)	28	Long-acting OCT 30 mg q28 days (n = 28) vs. long-acting OCT 30 mg q 21 days (n = 28)	— vs. 7%	— vs. 93%	—	—
	Anthony et al., (2011)	392	Overall population initial dose: long-acting OCT 20 mg: 49% vs. long-acting OCT 30 mg: 39%	6% (any dose)	57% (any dose)	—	—
	Chadha et al. (2009)	54	OCT (20 or 30 mg q month) (n = 24) vs. OCT high dose (40-90 mg) (n = 30)	—	—	—	(1 yr OS: 0.77 [95% CI, 0.50-0.91] vs. 0.88 [95% CI, 0.68-0.96] [*P* = 0.4777])
	Jann et al. (2013)	43	Long-acting OCT 30 mg: (n = 19) vs. long-acting OCT ≤ 20 mg: (n = 16) vs. OCT (dose NR) (n = 8)	5% (any dose)	37% (any dose)	—	98 mos (14-216)
Long-acting octreotide monotherapy vs. another monotherapy treatment							
	Wolin et al. (2015)	110	Long-acting PAS 60 mg (n = 53) vs. long-acting OCT 40 mg (n = 57)	2.0% vs. 1.9% Comparison NR	70.6% vs. 73.1% Comparison NR		
	Creutzfeldt et al. (1991)	33	IFN-α2c (2 × 106 IU/m2 QD) (n = 17) vs. OCT (200 µg TID, 500 µg TID if PD (n = 16)	—	85.7% vs. 37.5% Comparison NR		
	Bongiovanni et al. (2016)	30	Long-acting OCT 30 mg q 28 days (n = 20) vs. LAN 120 mg q 28 days (n = 10)	—	—	11.1 mos (95% CI, 7.0-15.2) vs. 10.1 mos (95% CI, 4.3-17.0) (*P* = 0.769)	—
Combination therapy vs. octreotide alone							
Radiant-2	Pavel et al. (2011), primary analysis	429	Everolimus 10 mg + long-acting OCT 30 mg (n = 216) vs. long-acting OCT 30 mg (+ PBO) q 28 days (n = 213)	4% vs. 12% Comparison NR	84% vs. 81% Comparison NR	16.4 mos (95% CI, 13.7-21.2) vs. 11.3 mos (8.4-14.6) HR, 0.77; 95% CI, 0.59-1.00; one-sided log rank test *P* = 0.026	—
Radiant-2	Anthony et al. (2015), subanalysis (prior SSA use)	429	Everolimus 10 mg + long-acting OCT 30 mg (Previous SSA use [n = 173]) Long-acting OCT 30 mg (+ PBO) (Previous SSA use [n = 166]) q 28 days	—	—	Previous SSA use: 14.3 mos (95% CI, 12.0-20.1) vs. 11.1 mos (8.4-14.6) HR, 0.81; 95% CI, 0.60-1.09; *P* = 0.077 SSA naive: 25.2 mos (95% CI, 12.0-not reached) vs. 13.6 mos (8.2-22.7) HR, 0.63; 95% CI, 0.35-1.11; *P* = 0.054	—
Radiant-2	Castellano et al. (2013), subanalysis (presence of colorectal NETs)	39	Everolimus 10 mg + long-acting OCT 30 mg (n = 19 with colorectal NETs) vs. long-acting OCT 30 mg (+ PBO) q 28 days (n = 20 with colorectal NETs)	67% vs. 37% Comparison NR	—	29.9 mos (95% CI, 5.6-not reached) vs. 6.6 mos (95% CI, 3.0-13.0) HR, 0.34; 95% CI, 0.13-0.89; *P* = 0.011	—
Radiant-2	Fazio et al. (2013), subanalysis (advanced lung NETs)	44	Everolimus 10 mg + long-acting OCT 30 mg (n = 33) vs. long-acting OCT 30 mg (+ PBO) (n = 11) q 28 days	0% vs. 0%	—	13.63 mos vs. 5.59 mos HR, 0.72; 95% CI, 0.31-1.68 *P* = 0.228	—
Radiant-2	Strosberg et al. (2015), subanalysis (post hoc analysis of OCT+PBO arm only)	196	Long-acting OCT 30 mg (+ PBO) q 28 days	—	—	Previous SSA: 11.1 (95% CI, 8.4-14.3) mos SSA naive: 13.6 mos (95% CI, 8.2-22.7) Comparison NR	Previous SSA: 33.5 mos (95% CI, 27.5-44.7) SSA naive: 50.6 mos (95% CI, 36.4-not reached) Comparison NR
	Arnold et al. (2005)	105	OCT SC 200 µg TID (n = 51) vs. OCT SC 200 µg TID + IFN-α 4.5 x 106 IU TID (n = 54)	2% vs. 9.3% Comparison NR	15.7% vs. 14.8% Comparison NR	6 mos vs. 6 mos Comparison NR	Comparison NR
	Kolby et al. (2003)	68	OCT SC 100 µg BID or up to 200 µg TID (n = 35) vs. OCT + IFN-α 5 x 106 units 5 days/week (n = 33)	—	—	—	[Mean 5-yr survival: 36.6% vs. 56.8%; HR 0.62; 95% CI, 0.33 to 116; *P* = 0.132]
	Strosberg et al. (2017)	229	177Lu-Dotatate 7.4 GBq q 8 weeks + OCT vs. OCT 60 mg q 4 weeks (n = 113)	18% vs. 3%; *P* < 0.001	—	Median PFS, 177Lu-Dotatate + OCT: not reached vs. OCT, 8.4 HR, 0.21; 95% CI, 0.13-0.33; *P* < 0.001	177Lu-Dotatate + OCT: 14 deaths vs. OCT: 26 deaths HR, 0.40; *P* = 0.004
Single-arm studies of octreotide for neuroendocrine tumors							
	Butturini et al. (2006)	21	OCT (100 µg TID for 2 weeks, then long-acting OCT acetate 20 mg on day 14 and then q 28 days until PD)	—	28%	41 mos	—
	Saltz et al. (1993)	34	OCT SC 50 µg BID to 150-250 µg TID	0%	50%	—	—
	Angeletti et al. (1999)	7	OCT SC 500 µg QID	14.3%	85.7%	—	—
	Anthony et al. (1993)	14	OCT SC 500-2,000 µg q 8 hours	31%	15%	—	—
	Arnold et al. (1996)	103	OCT SC 200-500 µg TID	0%	12.6%	—	—
	Arnold et al. (1993)	85	OCT 200 µg TID	4.4%	50%	—	—
	Bajetta et al. (2005)	31	Long-acting OCT 30 mg q 28 days	6%	52%	—	Not reached
	Chung et al. (2001)	10	Adjuvant long-acting OCT q month (specific dose NR)	—	—	—	(3-yr OS: 100%; 5-yr OS: 31%)
	di Bartolomeo et al. (1996)	58	OCT SC 500 µg (n = 23) or 1,000 µg (n = 35) Note: results not stratified by dosage	3%	47%	—	22 mos (1-32+ mos)
	Janson et al. (1993)	43	OCT SC 100 µg BID (median starting dose)	—	49%	—	—
	Panzuto et al. (2006)	31	Long-acting OCT 30 mg q 28 days	0%	47.6%	—	—
	Ricci et al. (2000)	15	Long-acting OCT 20 mg q 4 weeks	7%	40%	—	—
	Shojamanesh et al. (2002)	15	OCT SC 100-200 µg q 12 hours; long-acting OCT 20-30 mg q month	6%	47%	—	—
	Tomassetti et al. (2000)	16	Long-acting OCT 20 mg q 28 days	0%	87.5%	—	—
Different octreotide dosing regimens but report only overall results							
	Al-Efraij et al. (2015)	37	Long-acting OCT (40, 50, or 60 mg q month) (n = 37)	—	29% (any dose)	—	—
	Laskaratos et al. (2016)	254	Long-acting OCT 20 mg q 28 days (n = 198) or long-acting OCT 30 mg q 28 days (n = 56), depending on AEs	5% (any dose)	—	—	—
	Oberg et al. (1991)	22	OCT SC 50 µg BID for 6 months; dose increased to median 200 µg BID or TID	28%	36%	—	—
	Ramundo et al. (2014)	20	Long-acting OCT 30 mg q 28 days	—	80%	—	—
	Saglam et al. (2015)	23	Long-acting OCT 30 mg q 4 weeks	17.4%	60.9%	22.4 mos	70.1 mos
	Welin et al. (2004)	12	OCT SC 160 mg q 2-4 weeks (high dose)	—	SD for a median of 12 mos: 75%	—	37 mos
	Yuhong et al. (2016)	NR	Long-acting OCT dose and interval NR	—	79.6%	—	—

AE = adverse event; BID = twice daily; IFN = interferon; LAN = lanreotide; NR = not reported; PAS = pasireotide; PD = progressive disease; PFS = progression-free survival; q = every; QD = once daily; QID = four times daily; SC = subcutaneous; TID = three times daily; yr = year.

Discussion

- Based on this review, the strongest clinical trial evidence supporting octreotide's antitumor effect was in the phase 3, randomized, placebo-controlled PROMID clinical trial (Rinke et al., 2009; Rinke et al., 2017).
- Three retrospective observational analyses of overlapping periods of SEER-Medicare data provide the strongest retrospective evidence for an antitumor effect of long-acting octreotide, indicating that the use of long-acting octreotide was associated with significantly longer OS than no octreotide treatment among patients with distant metastases, and that standard dosing (21-30 mg) seems to be associated with better OS than low dose (≤ 20 mg) (Shen et al., 2014; Shen et al., 2015; Shen et al., 2016).
- A recently published review of escalated-dose SSAs in gastroenteropancreatic NETs by Chan et al. (2017) also found evidence of octreotide's antiproliferative effects.
- This study adds to previous reviews on this topic by broadening the search in multiple databases and not restricting by dose level, study type (i.e. clinical trial or retrospective study), or date of publication.

Conclusions

- The clinical trial and observational studies with informative evidence support long-acting octreotide's antitumor effect on time to tumor progression or OS. This review showed the rarity of existing studies assessing octreotide's antitumor effect. Future research in this area is warranted.

References

References available upon request.

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