What's New in Carcinoid Syndrome?

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10.12.13

Neuroendocrine Tumor Patient Education Conference

UCSF
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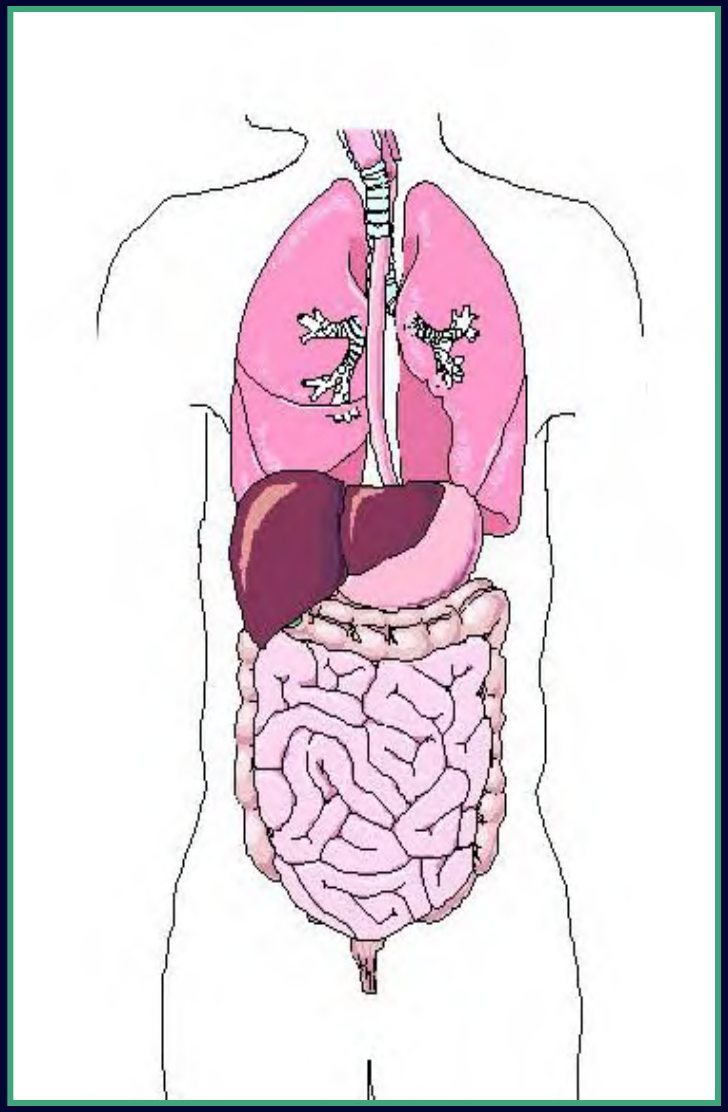
San Francisco

Overview

- Carcinoid Syndrome
- Management
- Special topics:
  - Refractory diarrhea
  - Carcinoid Crisis/Perioperative Management
  - Carcinoid Heart Disease
  - Cushing's syndrome

Carcinoid Tumors: Well-differentiated NET classified by site of origin



- **Foregut**
  lungs and bronchi, stomach
- **Midgut :**
  small intestine, appendix, proximal large bowel
- **Hindgut:**
  distal large bowel, rectum

Classification of Carcinoid Tumors

Origin	Organ	Clinical syndrome*	Behavior when metastatic
Foregut (33%)	Thymus Respiratory tract	Carcinoid syndrome, wheezing, rarely Cushing's syndrome or acromegaly	Relatively aggressive
	Stomach Duodenum	Flushing, gastrin hypersecretion, diarrhea, and Cushing's syndrome (5HIAA often normal)	
Midgut (34%)	Jejunum Ileum Appendix Cecum	Carcinoid syndrome Carcinoid syndrome Rare Carcinoid syndrome	Relatively indolent (+/-Obstruction from 1°, mesenteric fibrosis/ ischemia)
Hindgut (14%)	Descending colon Rectum	Rare Rare	Relatively aggressive

*From 5-HIAA, ACTH, histamine, 5-HTP, substance P, ACTH, etc.

Boudreaux, et al. Pancreas, 2010; 39; 753-766; Phan et al. Pancreas 2010; 39: 784-798.
Kulke et al. Pancreas, 2010; 39: 735-752

Carcinoid Syndrome

- Occurs in a subset of patients (10%?)
- Hormone-mediated symptoms (carcinoid syndrome) caused by secretion of serotonin and other neuropeptides into systemic circulation
- Triggered by stress, alcohol, exercise and certain foods

- Episodic symptoms:
  - Abdominal pain
  - Flushing* (light pink to deep red– usually face/chest)
  - Diarrhea*
  - Wheezing*/shortness of breath
  - Palpitations
  - Atypical: deep purple flush, shortness of breath, tearing

- Right-sided valvular heart disease
- Pellagra (dementia, diarrhea, dermatitis– skin findings)

*”Classic” syndrome is actually rare

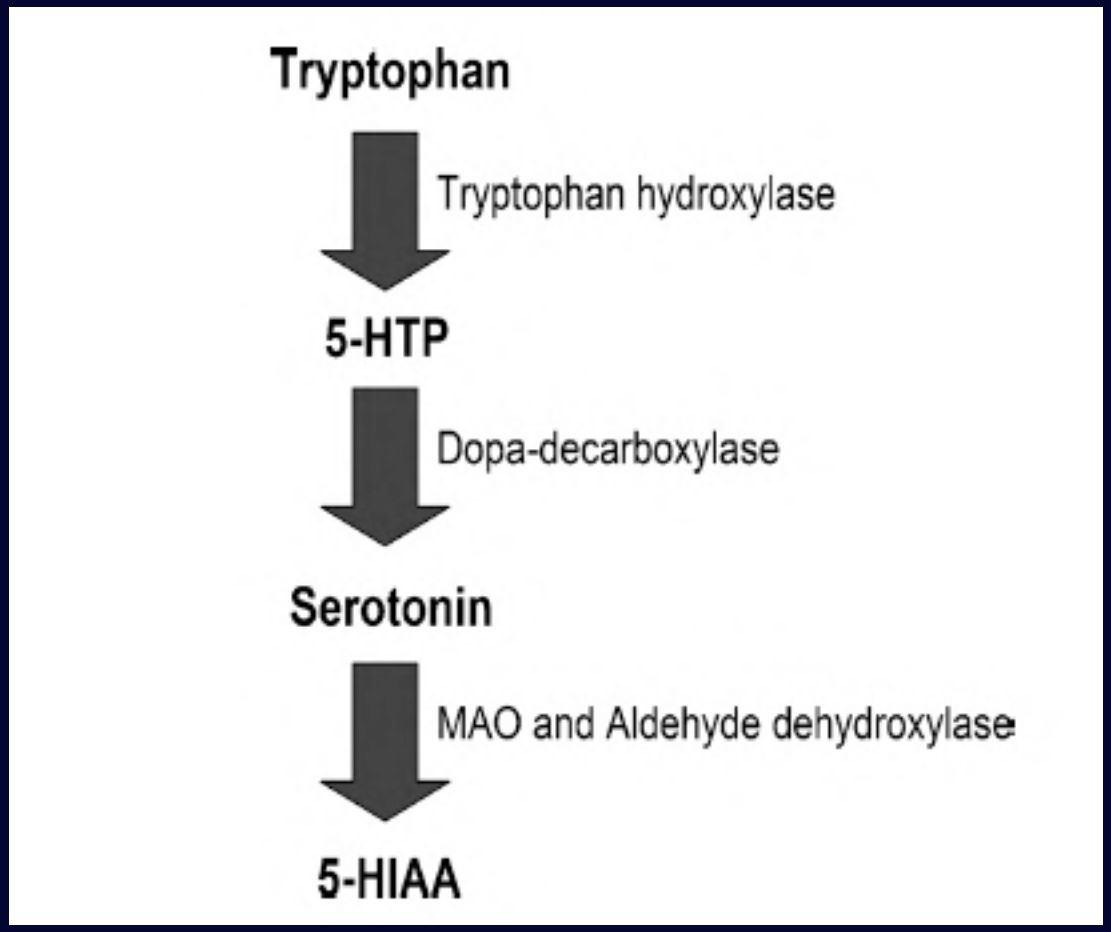
Carcinoid syndrome

- Serotonin is the classic cause of carcinoid syndrome, but a number of other vasoactive peptides may contribute:
  - Histamine (bronchospasm, flushing?)
  - Kinins (e.g. bradykinin)
    - Low BP, bronchospasm, flushing
  - Tachykinins
    - Includes substance P, VIP, neurokinin A
    - Flushing? Cardiac effects?

- *Specific symptom complex depends on site of origin / hormone(s) produced, and varies from patient to patient*

Mancuso, et al. J of Clinic Anesthesia, 2011 Vinik, et al. Pancreas, 2009

Synthesis of 5-HIAA



Vinik, et al. Pancreas, 2009

- Serotonin levels vary widely during day
- 5HIAA is urinary breakdown metabolite of serotonin
- In carcinoid syndrome, 5HIAA
  - 70% sensitivity
  - 90% specificity
  - Levels don't correlate with severity of syndrome
  - Pt can have syndrome w/o high 5HIAA (rare)

O-Toole, et al. Neuroendocrinology, 2009

Biochemical Testing

- Serum chromogranin (CGA)-elevated in 60-90%
  - Off PPI x 1-2 wk (substitute H2 blocker?), fasting?
  - Consistent timing w/r/t SSTa
  - False (+): impaired renal function, PPI, pregnancy, atrophic gastritis, steroids
  - limited agreement between different immunoassays
- Urinary 5HIAA (less variability than serotonin)
  - Artificially high: celiac, Whipple's disease, after eating tryptophan-rich foods/supplements
  - Avoid for 72 hr before, and during collection:
    - Bananas, walnuts, avocados, caffeine, plums, eggplants, plantains, tomatoes, pineapples, kiwis,
    - phenacetin, cold remedies with expectorants, phenathiazines

O'Toole, et al. Neuroendocrinology, 2009

Phan, et al. Pancreas, 2010

Biochemical Testing

- Plasma 5HIAA (nl <22 ng/ml)-NEW
  - Fast overnight
  - Collect in special tube
  - Correlates with urinary 5HIAA

Tellez, et al. Pancreas. 2013 Apr;42(3):405-10

Biochemical Testing

- Other potential markers:
  - Neuron specific enolase
  - Pancreastatin
  - Substance P
  - Neurotensin
  - Chromogranin B/C
  - Neurokinin A

Not widely available; less clinical applicability

Phan, et al. Pancreas, 2010

Carcinoid Syndrome

MANAGEMENT:

Somatostatin (SST)

- Bioactive neuropeptide (discovered in 1973-Nobel prize)
- Mediates inhibitory effects thru 5 receptors (SSTR 1-5)
  - Expressed throughout CNS, GI tract, endocrine/ exocrine glands, & immune/inflammatory cells
- Produced and acts locally :
  - ↓Glandular and exocrine secretions:
    - Inhibits GH/ACTH/TSH release
    - Pan-inhibitor of GI tract hormone release (insulin, glucagon)
    - Inhibits release of gastric acid, amylase
  - Antiproliferative

Schmid *et al*. *Mol Cell Endocrinol* 2008;286:69–74;

Regulatory Action of Somatostatin Receptors

Action	SST_1	SST_2	SST_3	SST_4	SST_5
Antisecretory		X	X		X
Anti-angiogenic		X	X		X
Antiproliferative/ Inhibit cell cycle (G1 arrest)	X	X	X		X
Induction of apoptosis	X	X	X		

Effects probably receptor- and tissue-specific

Adapted from Susini C, Buscail L and Weckbecker G, Lewis I, Albert R, et al.[1]

References: 1. Weckbecker G, Lewis I, Albert R, et al. *Nature Rev Drug Discov*. 2003, 2:999-1017. **2.** Öberg K, Kvols L, Caplin M, et al. *Ann Oncol*. 2004; 15:966-973. **3.** Susini C, Buscail L. *Ann Oncol*. 2006; 17:1733-1742.

SST Receptors and NETs

- Somatostatin receptors are highly expressed by NETs (>80%), which provides the rationale for clinical use of somatostatin analogs[1, 2]
  - Subtype expression varies between tumors (sst2 common)

- Targeting multiple somatostatin receptors confers direct and indirect antitumor effects[3, 4]

- *Activation of multiple somatostatin receptors has the potential to provide symptomatic, biochemical and disease control*

References: 1. Heaney AP, et al. Nature Rev Cancer. 2. Öberg K. Ann Oncol. 2004. 3. Susini C, et al. Ann Oncol.2006. 4. Weckbecker G, et al. Nat Rev Drug Discov. 2003.

Modlin et al. Alimentary Pharmacology & Therapeutics, 2009

Somatostatin analogs (SSTa) and NETs

SSTa indicated for the treatment of hormone-mediated sx[1]:

Octreotide (SQ)/Octreotide LAR (IM q mo)

- sstr 2, 5 (high) >sstr 3>sstr 1,4 (low)
- Sandostatin®, Sandostatin LAR®
- Approved for acromegaly and carcinoid syndrome

Lanreotide (SQ q 14d)/Lanreotide autogel (SQ q mo)

- sstr 2, 5 (high) >sstr 3>sstr 1,4 (low)
- Approved for acromegaly (Somatuline)

Pooled data suggests similar efficacy in NET[2]	**Symptom RR**	**Biochemical response**
Octreotide LAR	74% (62%-93%)	51% (28-77%)
Lanreotide autogel	68% (40-100%)	39% (18-58%)

1. Oberg et al. 2004. Ann Oncol; 15: 966—973

2. Modlin et al. Alimentary Pharmacology & Therapeutics, 2009

Antitumor activity

- PROMID study: Octreotide LAR treatment delays progression in treatment-naïve well-diff mid-gut carcinoids
  - Rinke, et al. 2009. J Clin Onc
- CLARINET study: Lanreotide delays progression in non-functioning well-mod diff GI and pancreatic NET
  - stratified for PD at entry
    - Caplin, et al. ESMO, 2013

Octreotide: Side effects

- Discomfort at injection site
- Altered glucose metabolism
- GI symptoms (may improve with time)
  - Loose stools
  - Abdominal cramping
  - Nausea
  - Flatulence
- Gallstones—up to 20% pt (usually asymptomatic)

- Consider periodic assessment of thyroid function, B12 level and Hgb A1C

Oberg, et al. Neuroendocrinology, 2009

What if symptoms persist?

- "bum" injection→ education!
  - Granulomatous reaction
- Reduced octreotide levels and/or tolerance to current dose
  - Increase octreotide LAR dose and/or add SQ for breakthru
    - 40% need "rescue" meds in initial trials
    - Approved up to 30 mg/mo (20-40% pt receive higher dose)
    - Value of 40 mg/mo? 60 mg/mo? 120 mg/mo?
  - Check octreotide level?
    - Controversial, but data suggest levels ↓ over time
    - Use to titrate dose
  - Change to continuous SQ infusion (controversial)
  - Change to novel SSTa (different SSTR coverage)

Woltering et al, 2008. Pancreas; Oberg et al. Neuroendocrinology, 2009; Boudreaux, et al. Pancreas, 1010

Future Directions: Control of hormone-mediated symptoms

- New delivery systems (e.g. octreotide implant)
- Other sstr2,5 agonists and pan-receptor agonists
- Subtype-specific SSTa
- Bi-specific SST analogs
- Hybrid SST/dopamine compounds (dopastatins)
  - D2R is often expressed in low grade NET
- Non-peptide analogs
  - Orally bioavailable? Longer $t_{1/2}$? Less immunogenicity?
- Serotonin synthesis inhibitors: Tryptophan hydroxylase (TPH) inhibitors

Modlin et al. Alimentary Pharmacology & Therapeutics, 2009

Current Clinical Trials: Phase III

Arms	Phase	Endpoint
Somatuline Depot (lanreotide 120 mg) SQ vs placebo in patients with a h/o carcinoid syndrome (ELECT study)– ASCO GI 2014?	III	Use of SQ rescue octreotide to control symptoms during the DB phase of study
Pasireotide LAR vs octreotide LAR IM Uncontrolled carcinoid syndrome on SSTa	III	Symptom RR
TELESTAR: telotristat for patients with carcinoid syndrome not adequately controlled by SSA	III	Change in #daily BM

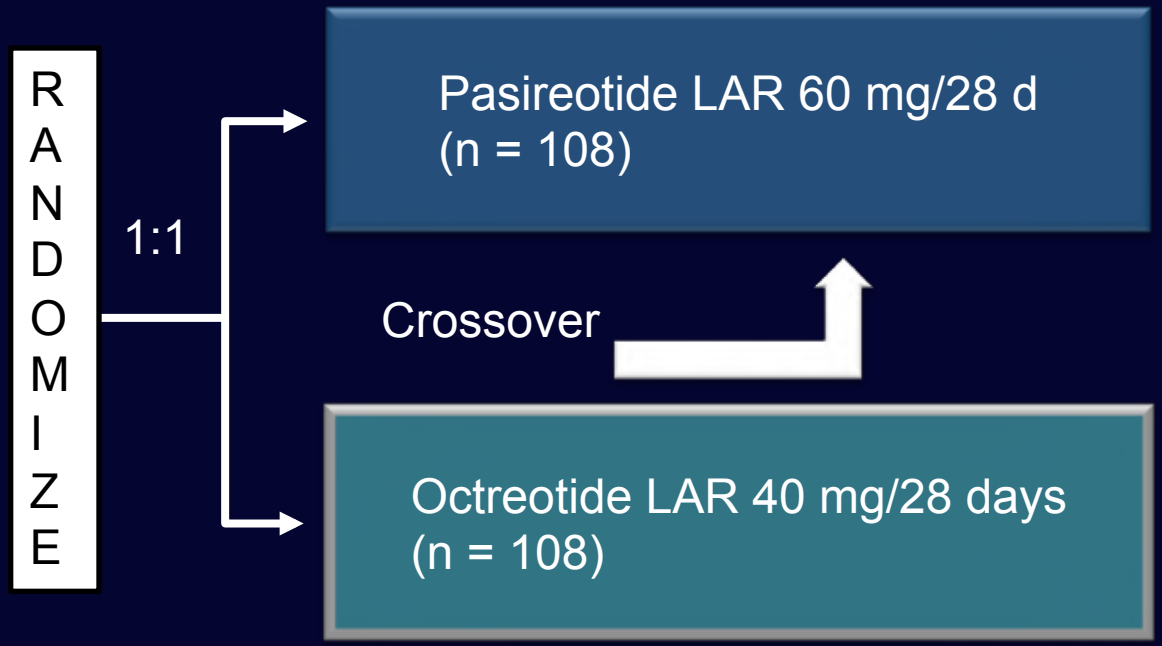
Panreceptor agonist: Pasireotide (SOM230)

- Binds sstr1,2,3,5 with high affinity (not sstr4)
- 30-, 5- and 40x ⇧affinity for $sstr_{1,3,5}$ and slightly ⇩affinity for $sstr_2$ than octreotide[1]
- Enhanced therapeutic efficacy?
  - option for patient with NETs refractory to octreotide[3]
  - similar or greater antiproliferative effects than octreotide[4]
  - Phase II study in GEP-NET pt with diarrhea/flushing inadequately controlled on octreotide LAR: symptom control in 27% using SQ BID formulation

1. Bruns C *et al. Eur J Endocrinol* 2002;2. Schmid *et al. Mol Cell Endocrinol* 2008 3. Ono K *et al. Anticancer Res* 2007 4. Kvols et al. J Clin Oncol, 2006;24:198s

Phase III Randomized, blinded study in patients with refractory carcinoid symptoms inadequately controlled by somatostatin analogs

- GI carcinoid
- Inadequate controlled disease-related symptoms on max approved dose of SSTa
- Measurable disease by RECIST
- KPS≥60



Primary endpoint: Control of flushing and/or diarrhea at 6 months
Secondary endpoints: Tumor response, safety
Exploratory: PFS

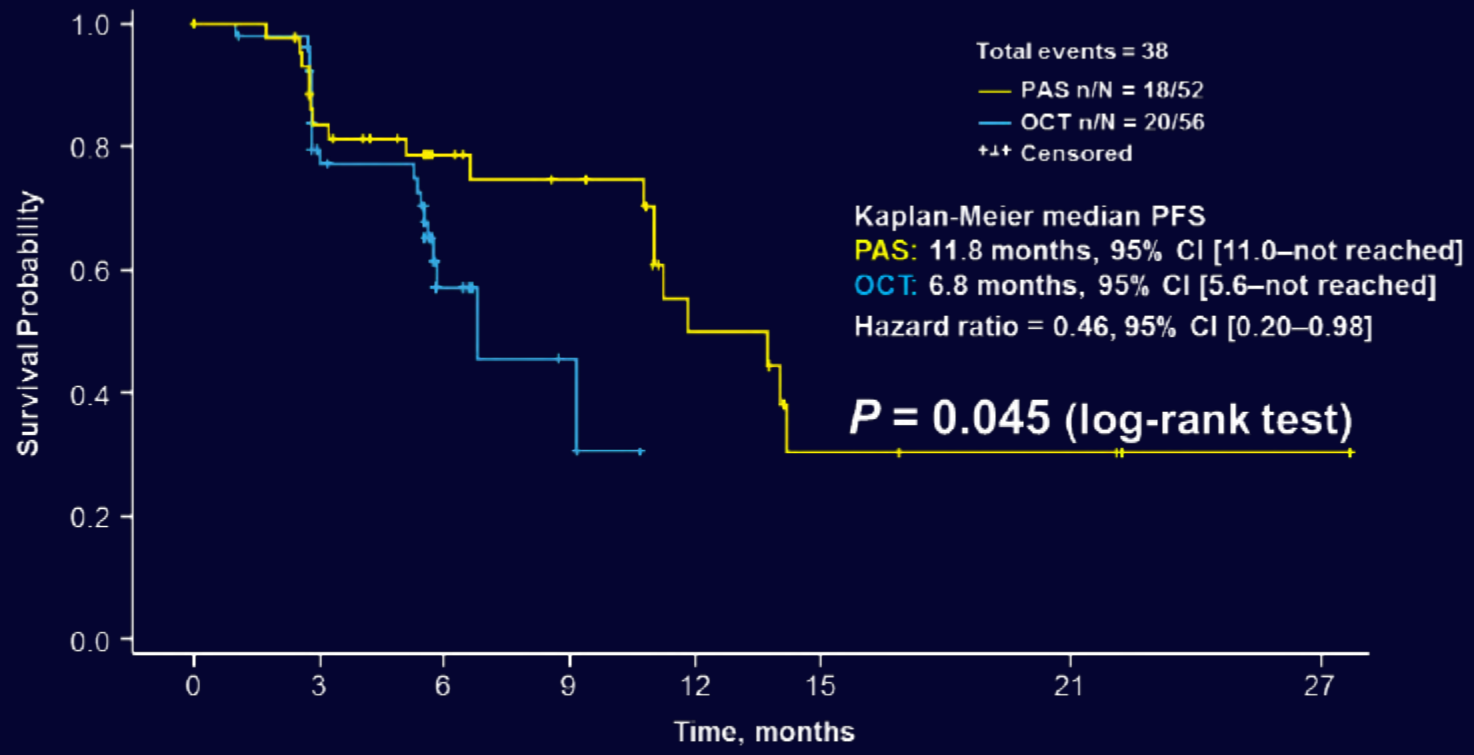
Wolin, et al. Proc ASCO, 2013

Phase III Randomized, blinded study in patients with refractory carcinoid symptoms inadequately controlled by somatostatin analogs

- Stopped early due to futility in 11/2011 (N=110 pt, 53 in pasireotide; 57 octreotide)
- Baseline characteristics balanced
- No difference in RR for symptom control
- No difference in disease control (CR+PR+SD) or radiographic RR

Wolin et al. Abstract 4031: poster presented at ASCO; May 31-June 4, 2013; Chicago, IL.

Phase III Randomized, blinded study in patients with refractory carcinoid symptoms inadequately controlled by somatostatin analogs



Time (months)	0	3	6	9	12	15	21	27
PAS	52	35	22	18	9	4	3	1
OCT	56	34	10	3	0	-	-	-

CI, confidence interval; OCT, octreotide LAR; PAS, pasireotide LAR; PFS, progression-free survival.

- Pasireotide LAR prolonged median PFS by 5 months by local investigator assessment compared to octreotide LAR treatment based on the exploratory analysis

Wolin et al. Abstract 4031: poster presented at ASCO; May 31-June 4, 2013; Chicago, IL.

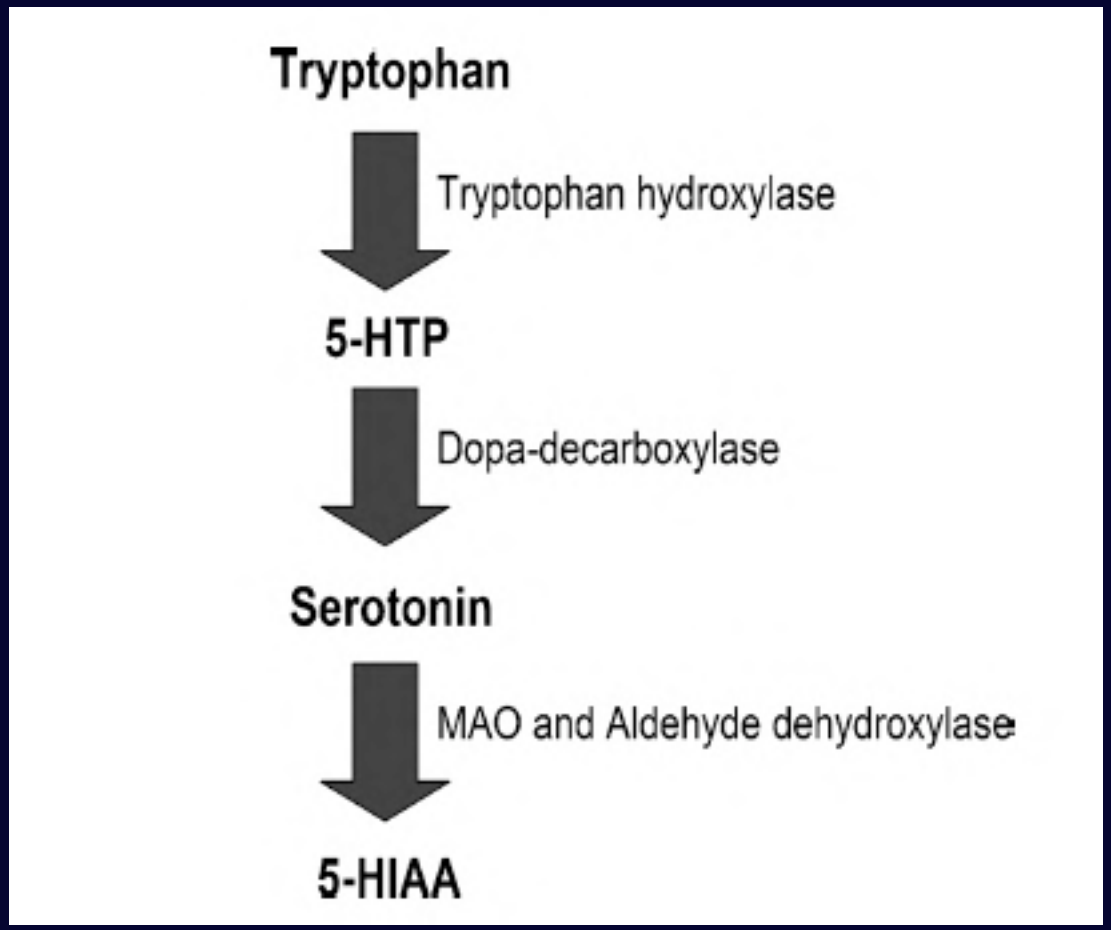
Phase 3 Study of Pasireotide LAR vs Octreotide LAR in Patients With Metastatic NETs With Disease-Related Symptoms Inadequately Controlled by Somatostatin Analogs

Conclusions

- Terminated early due to futility w/r/t symptom control
- Pasireotide LAR treatment ↑PFS by 5 months (investigator-assessed) compared to the octreotide LAR treated patients
- With the exception of hyperglycemia, safety profiles of pasireotide LAR and octreotide LAR similar
  - pasireotide treated patients had a higher frequency of hyperglycemia resulting in two treatment discontinuations
- Results support investigation of antitumor activity of pasireotide LAR

Wolin et al. Abstract 4031: poster presented at ASCO; May 31-June 4, 2013; Chicago, IL.

Synthesis of 5-HIAA



Vinik, et al. Pancreas, 2009

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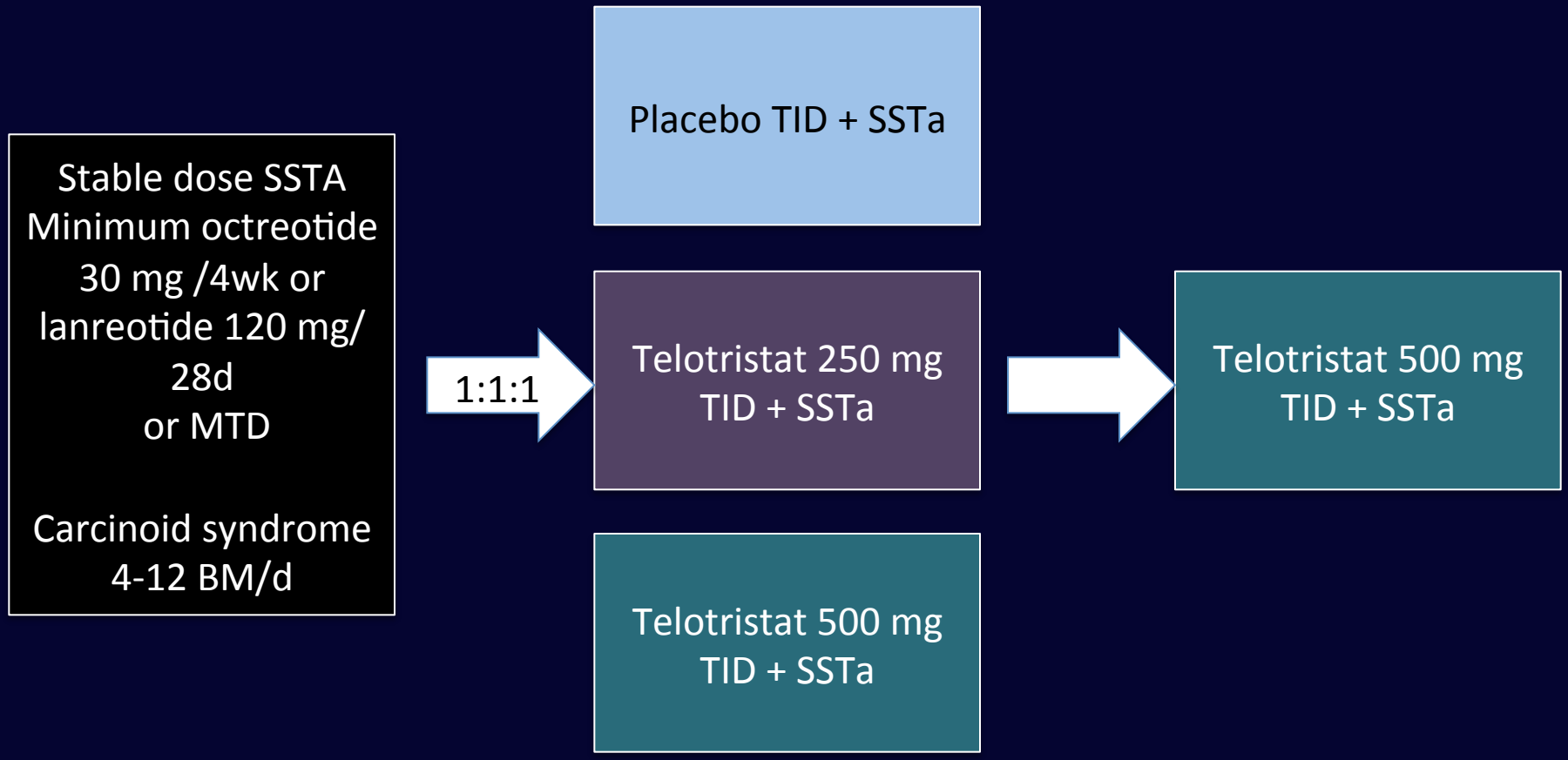
O-Toole, et al. Neuroendocrinology, 2009

Phase II trials of LX1606 (tryptophan hydroxylase inhibitor) in pt with carcinoid syndrome refractory to stable SSTa

- European study (open label, dose escalation):
  - 46% mean reduction in BM from baseline (P<0.001)
  - Urinary 5HIAA reduced from baseline: 68.3% at 8 wk (p=.019), 72.7% at 12 wk (p=.031)
    - Wiedenmann, et al. ASCO GI, 2012
- Randomized phase II (N=23, 18 on telotristat)
  - 33% reported control week 1; 46% week 4
  - 9/16 (56%) experienced a biochemical response and 5/18 (28%) experienced a clinical (BM) response (none of the placebo pt experienced response)
    - Kulke, et al. Proc ASCO, 2012

Phase 3 Study : Telotristat Etiprate in carcinoid (TELESTAR) -open 2013



Refractory Carcinoid Syndrome

- Add or change to interferon
  - 30-40% biochemical response
  - RR <10%
  - No clear dose-response relationship
- Liver directed
  - Surgical resection/ablation
  - Other liver-directed approaches (e.g. SIRT, HAE, HACE)
- Chemotherapy (unproven benefit)—RR <20% in most trials
- Peptide receptor radiotherapy
  - Not readily available in US (CLINICAL TRIAL)
  - Symptom control, SD, and/or radiographic responses reported in 4-30%
- Novel agents? (Inhibitors of VEGF? mTOR? Not FDA-approved)

Boudreaux, et al. Pancreas, 2010
Strosberg, et al. Cancer Control, 2011; 18: 127-137

http://www.nccn.org/index.asp

Carcinoid Syndrome

SPECIAL TOPICS

Refractory Diarrhea

- r/o refractory tumor
  - Rx: trial of SQ rescue, increased dose/frequency LAR (+/- monitor SSTa levels)
- r/o pancreatic exocrine insufficiency (from SSTa)
  - Fat malabsorption (foul-smelling stools that float)
  - Rx pancreatic enzymes w/ meals
- r/o pellagra due to niacin deficiency
  - Diarrhea, dementia, rash
  - Rx niacin supplement
- r/o short bowel syndrome s/p surgery (Rx cholestyramine?)
- Antidiarrheal (e.g. loperamide or tincture of opium)
- Serotonin receptor antagonists (improve diarrhea, not flushing)
  - 5-HT-1/2: cyproheptadine (ketanserin/methysergide?)
  - 5-HT-3: ondansetron

Phan, et al. Pancreas, 2010

Carcinoid Crisis

- Can be life threatening
  - Medialert bracelet!

- Spontaneous or triggered by stress, embolization, surgery, meds (e.g epinephrine), etc
  - High or low BP
  - Irregular/rapid heartbeat
  - Wheezing
  - Prolonged flushing
  - Shortness of breath
  - Poor tissue perfusion

– Octreotide is the mainstay of treatment

Mancuso, et al. J of Clinic Anesthesia, 2011

Carcinoid Crisis: Perioperative Management

- PREVENTION is the best treatment! Even with minor procedures
- Preop anesthesia evaluation
  - Low threshold for cardiac evaluation
- Perioperative octreotide drip (IV)
  - Some centers start 24 hr before surgery
  - Wean to off after a few days
  - 250-500 mcg sq for minor procedures; add 100-500 mcg/hr IV continuous drip for major procedures
- Avoid epinephrine if possible
- Fluid support
- Additional medications as indicated

Mancuso, et al. J of Clinic Anesthesia, 2011

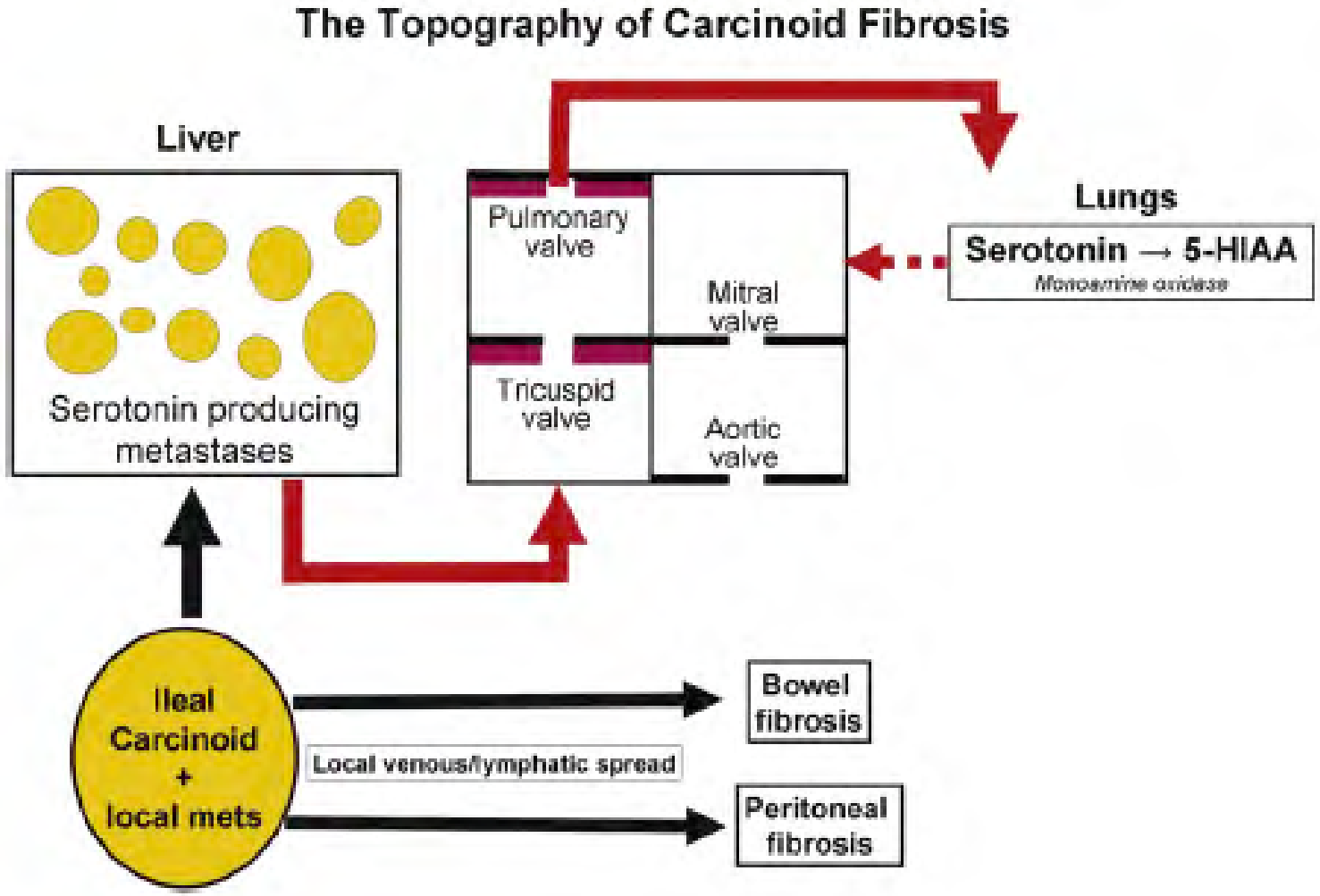
Medical Management of Carcinoid Syndrome	
Somatostatin analog	Inhibits hormone secretion
Anxiolytics	Inhibit stress-induced release of serotonin
H1 and H2 blocker	Block histamine
Bronchodilators	Reduce wheezing
H2 blocker, benadryl, steroids	Inhibit bradykinin
Aprotinin	Inhibit kallikrein (to treat refractory hypotension; flushing)
Cyproheptadine	Anti-serotonin and antihistamine effects

Mancuso, et al. J of Clinic Anesthesia, 2011

Carcinoid Heart Disease

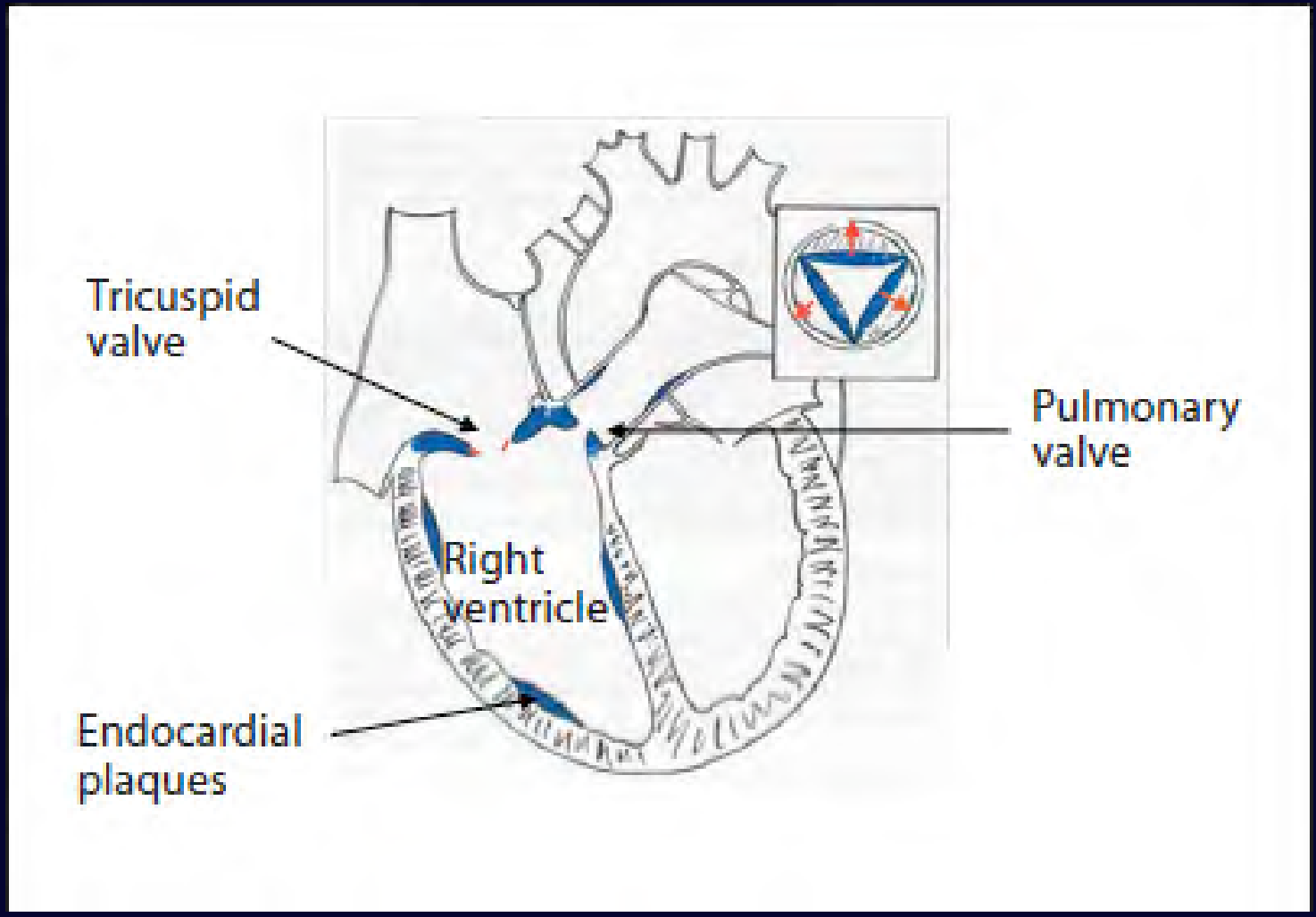
- Lower extremity swelling, weight gain, fatigue, enlarged liver
- Occurs in setting of carcinoid syndrome
  - Serotonin initiates fibrosis
  - Pulmonic and tricuspid valve dysfunction
    - Usually tricuspid regurgitation and pulmonic stenosis
  - Rarely left side involvement (unless bronchial involvement)
  - Rarely angina/vasospasm
- Initial presentation in up to 20%; eventually in up to 40% (usually late manifestation)
- Echocardiogram diagnostic
- Risk appears to correlate with 5HIAA levels

Modlin et al, International J Cardiology, 2008; Dobson, et al Endocrine Rel Cancer, 2013



Modlin et al, International J Cardiology, 2008

Carcinoid Heart Disease



Plockinger, et al. Neuroendocrinology, 2009

Carcinoid Heart Disease

- Prognosis improving over time
- Medical Management:
  - Somatostatin analogs
  - Diuretics (e.g. furosemide)
    - Treats the symptoms, doesn't reverse the fibrosis
  - Cardiology evaluation
- *Valve replacement* in selected patients

Castillo, et al. Semin Cardiothorac Vasc Anesth, 2013;
Modlin et al, International J Cardiology, 2008
Askew and Connolly, Curr Treat Options Cardiovasc Med, 2013

Carcinoid Syndrome: Cushing's Syndrome

- ACTH (adrenocorticotropic hormone) production leading to ⇧cortisol
- 1-2% bronchial carcinoids (and some PNET)
- Symptoms:
  - Easy bruising, poor healing
  - Diabetes
  - HTN
  - Weight gain
  - Depression/anxiety
- Treatment
  - Treat the underlying disease
  - Somatostatin analog trial
  - Block steroid biosynthesis
    - Ketoconzaole
    - Metyrapone
    - Mitotane
  - Bilateral adrenalectomy in selected patients

Phan, et al. Pancreas, 2010

Indications for therapy