Somatostatin analogs in the teatment of gastroenteropancreatic tumors

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Natural Somatostatin (1)

Peptide discovered by Brazeau in 1973.

It has been shown to:

- Inhibit hormone release
- Inhibit tumor growth in vitro
- Inhibit pancreatic enzyme secretion
- Impair gall bladder contraction and gastrointestinal motility

Inhibitory effect on secretion of peptide hormones

neuroendocrine tumors

Natural Somatostatin (2)

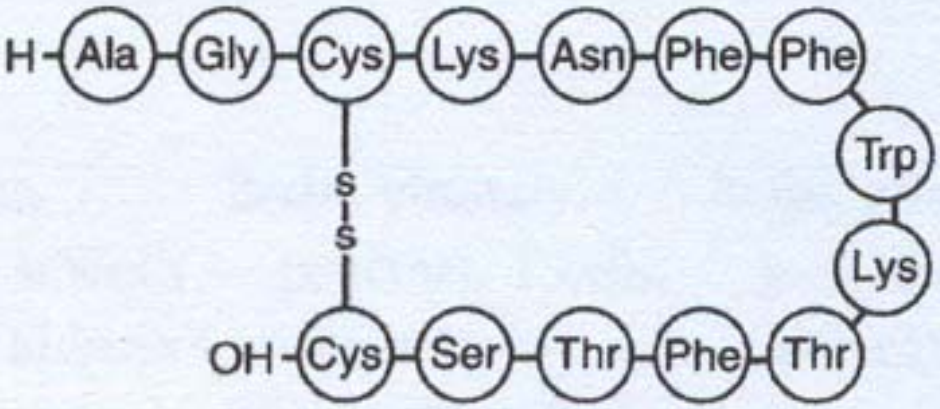
- Because of its short half-life (<3 min),

sst was inconvenient for clinical use

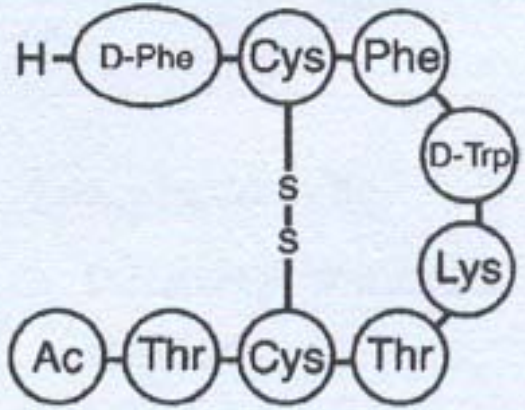
- Analogs were developed at the beginning of the 1980s

- Two of them, octreotide and lanreotide, are regularly used in clinics

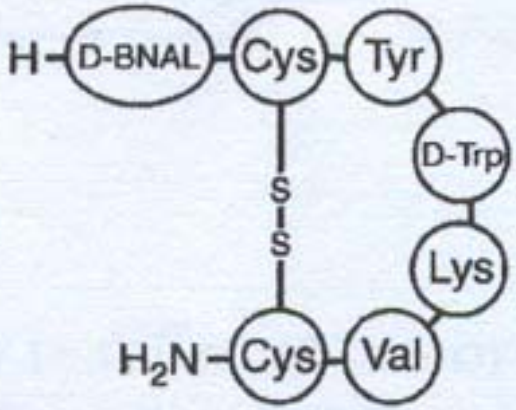
Chemical structure of native somatostatin-14 and the synthetic analogs



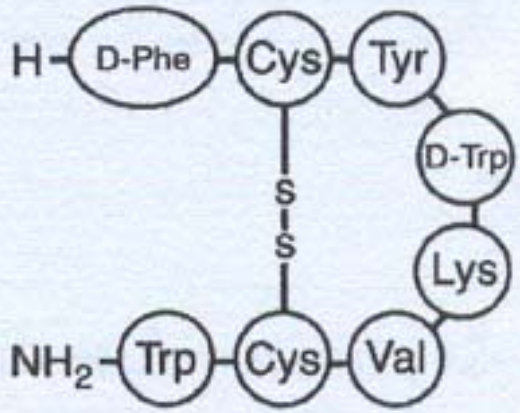
Native somatostatin-14



Octreotide



Lanreotide



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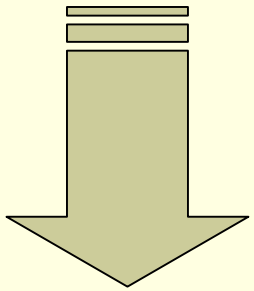
Goals of treatment (1)

The primary goal is to decrease hormone production and secretion



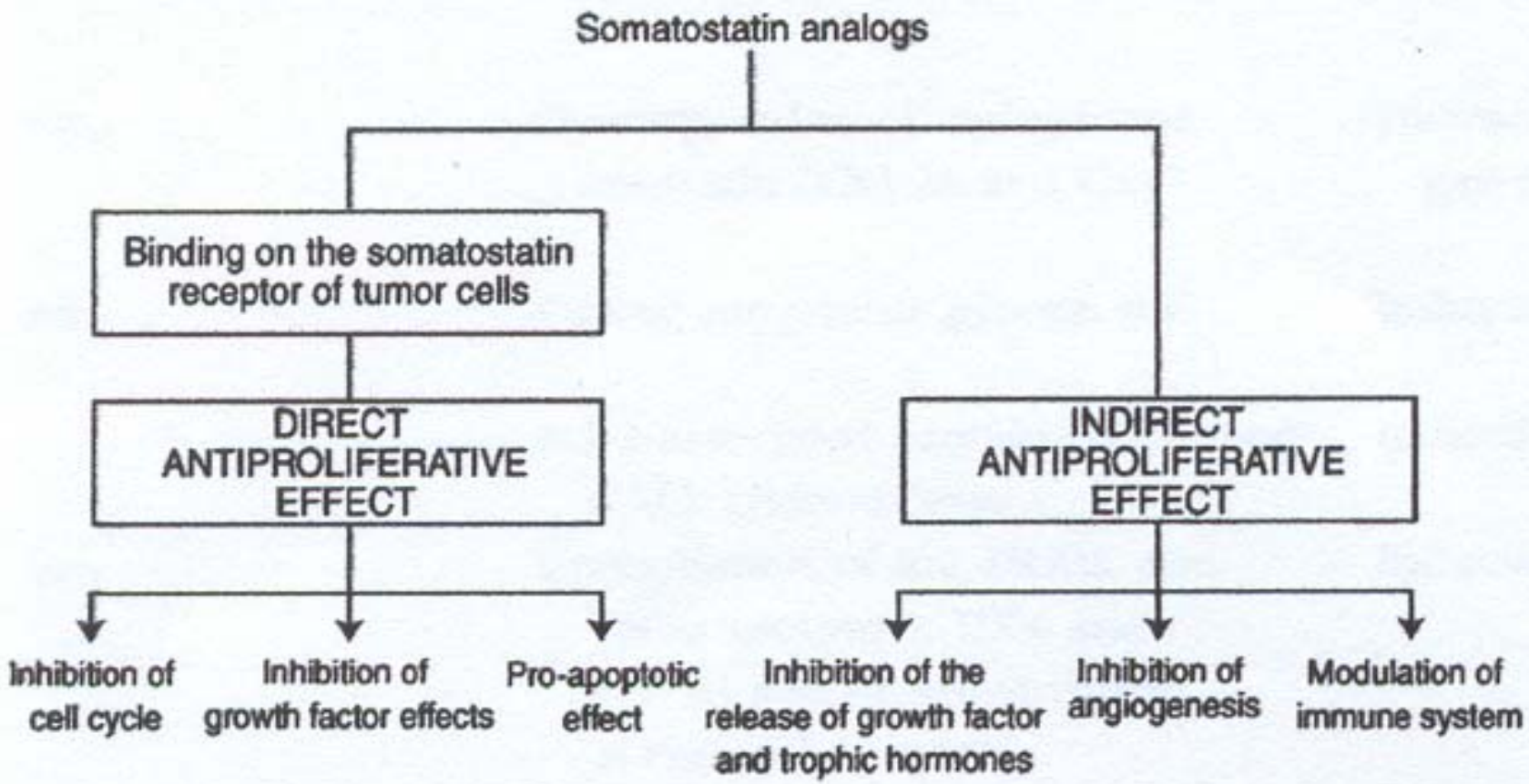
Control of hormone induced symptoms

Goals of treatment (2)

- Control tumor growth which may result in a stabilization of tumor size in treated patients
- Very high doses of somatostatin analogs may have a tumoricidal effect

Welin SV et al, Eur J Endocrinol 2004

Antiproliferative effects of somatostatin analogs on tumor cells



Iman H et al, Acta Oncol, 1997, Eriksson B. 2002

Somatostatin analog (1)

- When should somatostatin analog treatment be started?
- How should SSTa be prescribed for optimal symptom control?
- How should a patient on SSTa therapy be followed?

Somatostatin analog (2)

- How should octreotide be administered during invasive procedure ?
- What is the role of octreotide in patients receiving radiolabeled somatostatin therapy ?
- Do patients with GEP tumors develop drug resistance?

Somatostatin receptors

- Somatostatin acts through five different membrane receptors and induce different second messenger systems depending on which receptor is stimulated

- The reduction of hormone secretion is mainly mediated through SSTR2 and 5
- growth inhibition through receptors 1, 2 and 5
- apoptosis through receptors 2 and 3

Available SSTS analogs

- Short acting
  - Octreotide
- Long acting
  - Octreotide (Sandostatin LAR)
  - Lanreotide (Somatuline LA, Somatuline Autogel)

Octreotide - Lanreotide

Show

- high affinity for SSTR2
- Intermediate affinity to SSTR3 and SSTR5
- Low affinity for SSTR1 and SSTR4

Responses to SSTa therapy (1)

- They are defined according to three categories

  A. Symptomatic

  B. Biochemical

  C. Objective (radiologic)

Responses to SSTa therapy (2)

A. Symptomatic responses (up to 90%)

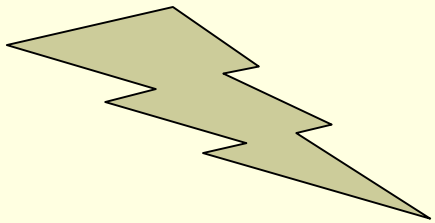
are reduction in hypersecretion related/hormonally mediated symptoms such as diarrhea, hypoglycemia

- In non-functional NETs they are: reduction in tumor bulk-related symptoms such as upper abdominal pain and improvement in quality of life or performance status

Responses to SSTa therapy (3)

B. Biochemical responses (up to 70%)

are defined as a ≥50% decrease in tumor markers



- The importance of biochemical responses is controversial.
- An early and dramatic reduction in markers may ported a more durable response to analogs

Responses to SSTa therapy (4)

C. Objective responses:

- Stable disease is observed, after initiation of treatment, in about one-third of the patients who show progressive disease before somatostatin analog therapy
- Tumor shrinkage was demonstrated in a small percentage

NETs response to SSt analog treatment

Response	Standard dose (%) 100–1500 mg/d	High dose (%) >3 mg/d	SR (%) 20–30 mg/ 2–4w
Subjective	64	42	63
Biochemical	63	75	67
Tumor	5	13	3

Anthony L et al, Acta Oncol, 1993, Faiss S et al, Digestion 1999, Welin SV, EJE 2004

Comparative features of octreotide and lanreotide

	Octreotide	***Lanreotide***
Reduction of diarrhea	50%	45%
Reduction of flushing	68%	54%
Most common adverse events	Gastrointestinal disorders Biliary disorders Injection site pain	Gastrointestinal disorders Biliary disorders Injection site pain
Availability of short acting formulation	yes	no
Frequency of administration	4 weeks	2 & 4 weeks

O' Toole et al Cancer 2000, Ricci et al Am J Clin Oncol, 2000

SSTR scintigraphy

- All patients with GEP tumors that are considered for somatostatin analog treatment should undergo SSTR scintigraphy, to establish their tumors SSTR status
- If the SSTR scintigraphy is negative other treatment options should be considered
- More than 80% of patients with a positive SSTR scan respond to somatostatin analog treatment

When should SSTa treatment be started?

- The accepted indications for the use of SSTa include:

  - Patients with peptide/amine-induced syndromes with clinical symptoms

  - Patients with progression of metastatic disease even without a syndrome

How to start treatment

- Start with short-acting octreotide for 2-3 days followed by injection of the long-acting analog

  In that way, patients with intolerable side-effects are prevented from receiving a long-acting injection

- Patients with very severe hormone induced symptoms may need a supplement of short-acting analog during the first weeks of treatment until plasma concentrations of the long-acting analog has reached therapeutic levels

Intavenous SSTa

- i.v administration of octreotide should be considered during certain invasive procedures, such as liver embolization and surgery
- Patients experiencing massive hormone secretion (carcinoid crises, WDHA-syndrome) should also be considered for iv infusion
- All patients should receive supplement therapy with pancreatic enzymes to avoid mal absorption diarrheas

Oberg k et al. Concensus report…….Annals of Oncol 2004

Long acting analogs

- The majority of patients will prefer the convinience of once monthly injection with the long acting formulations
- Most patients are initially treated with the 20mg of LAR.
- The LAR doses range from 20 to 60mg every 28 days

Oberg k et al. Concensus report….Annals of Oncol 2004

- Somatuline 60, 90, 120 mg

Long acting analogs

- Supplementary administration with the IR form of octreotide in patients escaping anti-secretory response is often required during long term treatment with LAR

- If it is necessary to give the patient rescue doses of IR octreotide three or four times per week increase in LAR dose to 30/4 weeks or reduce the interval between administration of LAR

Side effects of somatostatin analogs

- Most patients tolerate treatment very well
- Side effects are usually mild
- Usually diminish during the first few days of treatment

  Abdominal cramps, nausea and flatulence, loose stools, mild steatorrhea
- Impaired glucose tolerance
- Development of gallstones

Intolerance – Resistance (1)

- Some patients develop intolerance to octreotide or lanreotide. In these cases it might be worth trying the other analog

- For patients who develop resistance to treatment a switch to the other analog might prove useful

Intolerance – Resistance (2)

- 15 patients with progressive metastatic NETs who had experienced a prior response or disease stabilization with lanreotide 30 mg/14 d

All patients had measurable disease

- Octreotide LAR, i.m, 20 mg/4 weeks, 7 months
- Results:
- Symptomatic response rate → 82%
- Biochemical response → 41%
- Objective
  - partial response, 1 pt (7%)
  - stabilization of disease, 6 pts (40%)
  - progressive disease, 8 pts (53%)

Ricci S et al. Annals of Oncol, 2000

Follow-up (1)

- Biochemical parameters are repeated every 3-6 months

GEP NET patients: CgA, 24-h urine collection for determination of 5-HIAA

Pancreatic NETs: the predominant peptide should be measured

- Note: patients with non-functional GEP NET tumors may develop functional hormone secretion during tumor progression

Follow-up (2)

- Physical examination every three months
- Conventional imaging studies

  CT, MRI, U/S every six months
- Patients with progressive disease should be scanned before therapy and every 3 months until stability is seen for two consecutive imaging studies

Midgut carcinoid

- The largest group of patients with NET tumors that benefit from SSTSa treatment is midgut carcinoid tumors.
- Up to 80% will respond with a significant relief in symptoms
- Stabilization in tumor size has been reported in 24-57% of treated patients
- 5-10% respond with reduction in tumor size

SSTa + Radioisotopes

- Therapy with unlabeled octreotide should be stopped before the administration of radiolabed somatostatin analogs.
- Stop the IR form of octreotide for 24 h before radiotherapy
- For patients receiving LAR treatment should be interrupted >2 months berore radiotherapy. The patient can switch to the IR formulation

Oberg k et al. Concensus report…….Annals of Oncol 2004

SSTa + Interferon

- Generally they are proposed as single-agent therapy
- The combined use of these drugs was proposed in several non-randomized trials, indicating that there is an additive effect of the combination
- It could be indicated after progression to single-agent therapy

Fazio N et al, Annals Oncol, 2006

IFN-a/SST-analog combination therapy: published randomized trials

Author	No. pts	Arms	Results
			5-year-survey (%)
Kölby 2003	68	IFNα	36.6
	1991–98	OCT+IFNα	56.8
			1-year PFS (%)
Faiss 2003	80	IFNα	44.4
	1995–98	LAN	44
		IFNα+LAN	50 $p = 0.69$
			Median survival (months)
Arnold 2005	109	OCT	35
	1995–98	OCT+IFNα	51

10 centers

Liver metastases

metastases

PFS, progression free survival.

Octreotide - Lanreotide

Show

- high affinity for SSTR2
- Intermediate affinity to SSTR3 and SSTR5
- Low affinity for SSTR1 and SSTR4

Future - SOM 230

- Has the same inhibitory effect when binding to SSTR2 as octreotide
- Binds to SSTR1-3, SSTR5
- The effect mediated through SSTR1,3,5 is much stronger for SOM230

SOM 230 may have a stronger inhibitory effect than octreotide on hormone secretion from neuroendocrine tumor cells

Schmid HA et al, Neuroendocrinology 2004

Conclusions

- Treatment with somatostatin analogs reduces symptoms and hormone secretion in a majority of patients with functioning neuroendocrine tumors
- Stabilization of tumor growth may be achieved
- A reduction in tumor size can be achieved in few patients

Thank you for your attention

- Suppression test after administration of 100 µg octreotide s.c.
- >50% decrease in peptide / amine levels is seen 1-2 h after octreotide

- 31 patients, GEP with metastatic liver disease or distant metastases
- SSTa 6 months
- 45.2% stable disease for 26 months

Panzuto F et al, Ann Oncol, 2006