Somatostatin analogs in the treatment 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
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

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.
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 portend 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 SSSt analog treatment

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

## Comparative features of octreotide and lanreotide

<table>
<thead>
<tr>
<th>Feature</th>
<th>Octreotide</th>
<th>Lanreotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of diarrhea</td>
<td>50%</td>
<td>45%</td>
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<tr>
<td>Reduction of flushing</td>
<td>68%</td>
<td>54%</td>
</tr>
<tr>
<td>Most common adverse events</td>
<td>Gastrointestinal disorders, Biliary disorders, Injection site pain</td>
<td>Gastrointestinal disorders, Biliary disorders, Injection site pain</td>
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<tr>
<td>Availability of short acting formulation</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>4 weeks</td>
<td>2 &amp; 4 weeks</td>
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</tbody>
</table>

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 convenience 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
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%)

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 radiolabeled somatostatin analogs.
- Stop the IR form of octreotide for 24 h before radiotherapy.
- For patients receiving LAR treatment should be interrupted >2 months before 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

<table>
<thead>
<tr>
<th>Author</th>
<th>No. pts</th>
<th>Arms</th>
<th>Results</th>
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<tbody>
<tr>
<td>10 centers</td>
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<td>5-year-survey (%)</td>
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<tr>
<td>Kölby 2003</td>
<td>68</td>
<td>IFNα</td>
<td>36.6</td>
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<tr>
<td>Liver metastases</td>
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<td>OCT+IFNα</td>
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<tr>
<td>metastases</td>
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<td>1-year PFS (%)</td>
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<td>Faiss 2003</td>
<td>80</td>
<td>IFNα</td>
<td>44.4</td>
</tr>
<tr>
<td></td>
<td>1995–98</td>
<td>LAN</td>
<td>44</td>
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<tr>
<td></td>
<td></td>
<td>IFNα+LAN</td>
<td>50 p = 0.69</td>
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<td>Median survival (months)</td>
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<td>Arnold 2005</td>
<td>109</td>
<td>OCT</td>
<td>35</td>
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<tr>
<td></td>
<td>1995–98</td>
<td>OCT+IFNα</td>
<td>51</td>
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</tbody>
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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