ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Biotherapy

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Introduction

Biotherapy for neuroendocrine tumors essentially includes treatment with somatostatin analogues and α interferons (IFNs) [1–9]. A large number of tyrosine kinase, angiogenesis as well as mTOR inhibitors have recently been developed and also attempted in the treatment of neuroendocrine tumors, but these new agents will not be covered by these guidelines due to lack of data.

Somatostatin Analogues

These agents should be used according to earlier published guidelines. The main indication for the use of somatostatin analogues is treatment of functioning neuroendocrine tumors causing hormone-related clinical syndromes. Somatostatin analogues might block the release of various active agents that cause the clinical syndrome and thereby reduce the symptoms and improve quality of life. The drug has been discussed also for use in non-functioning neuroendocrine tumors, but available data are still contradictory and controversial. Randomized trials are ongoing.

What Is Necessary in Preparation for Somatostatin Analogue Treatment?

Basal investigations before biotherapy with somatostatin analogues include electrocardiogram (ECG) and ultrasound of the gallbladder. With regard to the biochemistry, blood cell count transaminases, bilirubin, blood glucose, electrolytes including Ca, P, creatinine and vitamin B12 should be analyzed. Besides that, blood pressure and body weight, TSH and ft4 should also be included in the standard evaluation. For evaluation of the disease, CgA, U-5-HIAA and other tumor markers, if indicated, should be measured and followed during treatment.

Patient Information

The patient information should include description of mechanism of action, side effects and how to react to adverse effects. The following drug interaction should be taken into consideration.

Bromocriptine: bioavailability of bromocriptine may be increased by octreotide.
Cyclosporine: reduction of serum cyclosporine levels have been recorded and cases of transplant rejection have been reported.

**Dietary Considerations**

For immediate release, preparation injections should be scheduled between meals to decrease gastrointestinal effects. Somatostatin analogues may alter absorption of dietary fats.

**Pregnancy**

Teratogenic effects have not been reported in animal studies, but octreotide crosses the human placenta, and data concerning use in pregnancy is limited.

*Lactation*: excretion in breast milk is unknown, use with caution. Follow the recommendations given by the pharmaceutical company.

**Initiation of Therapy with Somatostatin Analogues**

According to ENETS Guidelines and recommendations from the medical companies, the advice to initiate treatment with s.c. preparations instead of long-acting i.m. is recommended in new patients, to avoid long-lasting side effects by LAR preparations in a limited number of patients. As a general recommendation, octreotide s.c. could be given for a couple of days at a dose of 100–600 μg/day in 2–4 divided doses, then switch to i.m. injections with depot preparations. Octreotide LAR, 10–30 mg, every 3–4 weeks i.m. deep intragluteally. Lanreotide Autogel 60–120 mg deep s.c. every 4–6 weeks. Depending on the clinical response and the need for rescue medication with s.c. octreotide, dose adjustments can take place. Follow the ENETS Guidelines and rules given by the company.

**Dose Adjustment in Patients with Comorbidities**

In old age, elimination half-life is increased by 46% and clearance is decreased by 26%; dose adjustment may be required.

Renal impairment: severe renal failure requiring dialysis and clearance is reduced by 50%; might require specific dosing guidelines that are not available at the moment.

Intravenous applications of octreotide (preparation for surgery or carcinoid crisis), infusion with 50–100 μg/h with octreotide, continuing for 24–48 h depending on the type of surgery. Preoperative preparation bolus injection with 200 μg of octreotide s.c. 1 h before start of surgery and in selected cases 4 times 100 μg, 24 h before start of surgery. Avoid adrenergic substances. For further reading, see the surgical chapter.

**Monitoring of the Adverse Effects**

Check every 3 months for:

- Ultrasound: gallbladder, gallstones (not routinely, only when symptomatic)
- Lab: blood cell count, transaminases, bilirubin, blood glucose, electrolytes including Ca, P, creatinine
- Endocrinology: TSH, ft4, CgA, 5-HIAA or other relevant hormones
- Blood pressure: check every 6 months for ECG and vitamin B₁₂

**Adverse Events**

*Diarrhea/lose stools*: exclude other causes (bacterial overgrowth, short bowel syndrome, lactose intolerance, bile acid syndrome). Substitute with pancreatic enzymes or recommend loperamide.

*Sludge/gallstones*: add chenodesoxy – ursodesoxycholic acid until disappearance of sludge/gallstones.

*Vitamin B₁₂ deficiency*: substitute

*Hypothyroidism*: substitute

*Pain at injection site*: inject medication at room temperature and cool the injection site.

*Patients with diabetes mellitus* should be monitored closely when therapy is initiated. Adjustment of antidiabetic therapy might be necessary.

**Control of Therapeutic Efficacy**

Evaluate patients every 3–6 months.

*Biochemistry:*

- CgA
- 5-HIAA if indicated
- Other tumor markers

*Imaging:*

- CT or MRI every 6 months
- US of the abdomen if indicated, every 3 months
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**Documentation and Reporting of Results**

Use the RECIST criteria (see section on radiology).

**Interferon**

IFN is registered for treatment of midgut carcinoid tumor and the carcinoid syndrome in a majority of European countries. It has been attempted in more than 600 reported patients in different trials so far and the response rates have been good. Biochemical responses in 40–60%, symptomatic improvement in 50–60% and tumor responses in 10–15% of the patients. Earlier studies included human leukocyte IFN-α, but nowadays recombinant IFN-α2A and IFN-α2B and pegylated forms are the only ones that are in clinical use. For details about the use of IFN-α, see the recommendations from the ENETS Guidelines.

**Recommended Basal Investigations before Therapy with IFN-α**

ECG  
Chest X-ray  
Blood pressure  
Body weight  
Biochemistry: blood cell count, transaminases, bilirubin, albumin, prothrombin time, blood glucose, electrolytes, creatinine, triglycerides  
Endocrinology:  
- TSH  
- ft4  
- CgA  
- 5-HIAA or other tumor markers if indicated.

Treatment should not be used in patients with autoimmune diseases, such as rheumatoid arthritis, SLE and patients of very old age (>70 years), or with severe psychiatric disorders such as mental depression or psychosis.

**Patient Information**

Advise on:  
- Mechanism of action  
- Side effects  
- How to react to adverse effects  
For details, see the information given by the companies.

**Drug Interaction**

**Drugs**

Inhibits CYP1A2.  
Ribavirin: concurrent treatment may increase the risk of hemolytic anemia.  
Theophylline: IFN-α may increase the levels/effects of theophylline; monitor.  
Zidovudine: IFNs may decrease the metabolism of zidovudine; the neutropenic effects of zidovudine and IFN may be synergistic; monitor.

**Pregnancy and Lactation**

Safety and efficacy for use during pregnancy have not been established. During lactation IFN enters the breast milk. Go to the information of the pharmaceutical companies.

**Initiation of Treatment**

According to the recommendations of the pharmaceutical companies and the ENETS Guidelines. IFN-α2A (Roferon®) and IFN-α2B (IntronA®) could be given at doses 3–9 MU s.c. every second day, preferentially in the evenings. The standard dose is 3–5 MU. Pegylated IFN (Pegasys®, PegIntron®) are currently under evaluation at doses of 50–100 μg, once a week s.c.

**Dosage Adjustment**

Titrate according to symptoms (up to 5 MU/day s.c.), for safety reasons the white blood cell count should not be lower than 3 \( \times 10^9 \)/l. Increasing the dose to >12 MU/dose does not increase efficacy, but increases the number of side effects.

It is important to titrate the dose individually in each patient, because the treatment is intended to be long term and the patient’s quality of life is very important. IFN-α should be discontinued 3–4 weeks before surgery, but may be ongoing in severe cases, most often in combination with somatostatin analogues and monitoring of the adverse effects.

Check every 6 months for:  
- ECG, blood cell count, transaminases, bilirubin, albumin, prothrombin time, blood glucose, electrolytes, creatinine, triglycerides (every 3 months)  
- Endocrinology: TSH, ft4, CgA, 5-HIAA or other tumor markers if indicated (every 3 months)  
- Blood pressure  
- Body weight (every 3 months)  
At signs and symptoms of autoimmune disease, check relevant autoimmune parameters (RA-factor ANA and...
thyroid autoantibodies). Thyroid autoantibodies should be checked every 6 months. Hypothyroidism is a sneaking disease and can add to the side effects of the drug, such as chronic fatigue.

Fever and flu-like symptoms (chills, malaise, headache, myalgia, tachycardia) may occur within 1–2 h after application. Treat with paracetamol.

Autoimmune thyroid disease: treat accordingly
Diabetes mellitus: treat
Severe psychiatric disorders: end the treatment
Severe bone marrow depression: end the treatment
Severe weight loss: end the treatment
Severe hepatic disease: end the treatment
SLE, rheumatoid arthritis: end the treatment

Evaluation of therapeutic efficacy: evaluate patients every 3–6 months with biochemistry, CgA, 5-HIAA if indicated, other tumor markers if indicated.

Imaging: CT, MRI every 6 months, US every 3 months.

**Documentation and Reporting of Results**

Use the RECIST criteria. For various side effects refer to inserts with the compound.

**List of Participants**

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

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References


