

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

Kjell Öberg^a Diego Ferone^b Gregory Kaltsas^c Ulrich-Peter Knigge^d Babs Taal^e
Ursula Plöckinger^f and all other Mallorca Consensus Conference participants

^aDepartment of Internal Medicine, Endocrine Unit, Uppsala University Hospital, Uppsala, Sweden; ^bDepartments of Internal Medicine and Endocrinological and Metabolic Sciences, University of Genoa, Genoa, Italy; ^cG. Genimatas Hospital, Athens, Greece; ^dDepartment of Surgery, Rigshospitalet, Copenhagen, Denmark; ^eNetherlands Cancer Centre, Amsterdam, The Netherlands; ^fDepartment of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin, Germany

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 – ursodesoxycho-lic 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

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- α_{2A} and IFN- α_{2B} 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- α_{2A} (Roferon[®]) and IFN- α_{2B} (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 μ g, 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

Göran Åkerström, Department of Surgery, University Hospital, Uppsala (Sweden); Bruno Annibale, University Sapienza Roma, Rome (Italy); Rudolf Arnold, Department of Internal Medicine, Philipps University, Munich (Germany); Emilio Bajetta, Medical Oncology Unit B, Istituto Nazionale Tumori, Milan (Italy); Jaroslava Barkmanova, Department of Oncology, University Hospital, Prague (Czech Republic); Yuan-Jia Chen, Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing (China); Frederico Costa, Hospital Sirio Libanes, Centro de Oncologia, São Paulo (Brazil); Anne Couvelard, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); Joseph Davar, Department of Cardiology, Royal Free Hospital, London (UK); Wouter de Herder, Department of Internal Medicine, Section of Endocrinology, Erasmus MC, Rotterdam (The Netherlands); Gianfranco Delle Fave, Ospedale S. Andrea, Rome (Italy); Barbro Eriksson, Medical Department, Endocrine Unit, University Hospital, Uppsala (Sweden); Massimo Falconi, Medicine and Surgery, University of Verona, Verona (Italy); David Gross, Department of Endocrinology and Metabolism, Hadassah University Hospital, Jeru-

salem (Israel); Ashley Grossman, St. Bartholomew's Hospital, London (UK); Björn Gustafsson, Medisinsk avd, Gastroseksjon, St Olavs Hospital, Trondheim (Norway); Rudolf Hyrdel, II. Internal Medical Department, University Hospital Martin, Martin (Slovakia); Diana Ivan, Endocrinology and Diabetology, Klinikum der Philipps-Universität, Marburg (Germany); Reza Kianmanesh, UFR Bichat-Beaujon-Louis Mourier, Service de Chirurgie Digestive, Hôpital Louis Mourier, Colombes (France); Günter Klöppel, Institut für Pathologie, TU München, Munich (Germany); Paul Komminoth, Institute for Pathology, Stadtspital Triemli, Zürich (Switzerland); Beata Kos-Kudła, Śląska Akademia Medyczna Klinika Endokrynologii, Zabrze (Poland); Dik Kwekkeboom, Department of Nuclear Medicine, Erasmus University Medical Center, Rotterdam (The Netherlands); Rachida Lebtahi, Nuclear Medicine Department, Bichat Hospital, Paris (France); Val Lewington, Royal Marsden, NHS Foundation Trust, Sutton (UK); Anne Marie McNicol, Division of Cancer Sciences and Molecular Pathology, Pathology Department, Royal Infirmary, Glasgow (UK); Emmanuel Mitry, Hepatogastroenterology and Digestive Oncology, Hôpital Ambroise-Paré, Boulogne (France); Ola Nilsson, Department of Pathology, Sahlgrenska sjukhuset, Gothenburg (Sweden); Juan O'Connor, Instituto Alexander Fleming, Buenos Aires (Argentina); Dermot O'Toole, Department of Gastroenterology and Clinical Medicine, St. James's Hospital and Trinity College Dublin, Dublin (Ireland); Ulrich-Frank Pape, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); Mauro Papotti, Department of Biological and Clinical Sciences, University of Turin/St. Luigi Hospital, Turin (Italy); Marianne Pavel, Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany); Aurel Perren, Institut für Allgemeine Pathologie und Pathologische Anatomie der Technischen Universität München, Klinikum r.d. Isar, Munich (Germany); Marco Platania, Istituto Nazionale dei Tumori di Milano, Milan (Italy); Guido Rindi, Department of Pathology and Laboratory Medicine, Università degli Studi, Parma (Italy); Philippe Ruszniewski, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); Ramon Salazar, Institut Català d'Oncologia, Barcelona (Spain); Aldo Scarpa, Department of Pathology, University of Verona, Verona (Italy); Klemens Scheidhauer, Klinikum rechts der Isar, TU München, Munich (Germany); Jean-Yves Scoazec, Anatomie Pathologique, Hôpital Edouard-Herriot, Lyon (France); Anders Sundin, Department of Radiology, Uppsala University Hospital, Uppsala (Sweden); Waldemar Szpak, Westville Hospital, Mayville (South Africa); Pavel Vitek, Institute of Radiation Oncology, University Hospital, Prague (Czech Republic); Marie-Pierre Vullierme, Service de Gastroentérologie, Hôpital Beaujon, Clichy (France); Bertram Wiedenmann, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin (Germany).

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