

# ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Chemotherapy in Patients with Neuroendocrine Tumors

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## Introduction

Chemotherapy for neuroendocrine tumors includes treatment with combinations of streptozotocin (STZ) + doxorubicin and/or 5-fluorouracil (5-FU), cisplatin + etoposide and dacarbazine. Recently, some new chemotherapeutic agents have come into use, such as temozolomide, oxaliplatin, and capecitabine, but they will not be discussed here.

The decision to give chemotherapy should be based on criteria of primary tumor localization, stage and proliferation index as stated in the ENETS Guidelines. It should be emphasized that administration of chemotherapy may elicit hormonal crises.

## Combinations with STZ, Doxorubicin or 5-FU

The combination of STZ + doxorubicin or 5-FU should be given according to the ENETS Guidelines. The main indication for the use of this combination is treatment of malignant inoperable neuroendocrine pancreatic tumors with low to moderate proliferate capacity, when biother-

apy has failed. STZ is an alkylating nitrosurea compound, but the exact mechanism of its cytotoxicity is not known. 5-FU acts as an antimetabolite that inhibits thymidylate synthetase, causing depletion of thymidine which results in cell death. Doxorubicin binds to DNA, resulting in steric hindrance of DNA and RNA synthesis. Combination treatment with STZ + 5-FU or doxorubicin may reduce hormonal symptoms and result in an objective tumor response in 20–35% of patients.

### *What Is Necessary in Preparation for Combination Treatment with STZ + 5-FU/Doxorubicin?*

The patients should be asked about the following symptoms that might influence the decision: fever, cough, dysuria and diarrhea. Certain laboratory tests of blood and urine should be analyzed: blood counts, transaminases, bilirubin, albumin, creatinine clearance and blood glucose. Body weight and blood pressure should also be checked. If doxorubicin is given, the cardiac ejection fraction (EF) should be determined. An EF <40% precludes treatment. For evaluation of the disease, chromo-

granin A (CgA) and other specific tumor markers should be determined and followed during treatment.

#### Patient Information

The patient information should include description of action, side effects and how to react to adverse effects.

#### Dietary Instructions

Frequent small meals are recommended to maintain adequate nutrition.

#### Drug Interactions

The following drug interaction should be considered: doxorubicin toxicity may be increased with concurrent use of STZ and the doxorubicin dosage should be adjusted accordingly.

#### Pregnancy and Nursing Is Contraindicated

In younger patients:

Contraception is recommended.

Cryoconservation of sperm and tissue of the ovaries should be considered.

#### Initiation Therapy

According to the ENETS Guidelines.

In the combination of STZ + 5-FU described by Moertel et al. [1], STZ should be given at 0.5 g/m<sup>2</sup> together with 5-FU 400 mg/m<sup>2</sup> for 5 days every 6 weeks. STZ is administered as a short (30–60 min) infusion or rapid intravenous push and 5-FU is given as intravenous bolus injection (table 1).

When STZ is given in combination with doxorubicin, STZ is administered at 0.5 g/m<sup>2</sup> for 5 days every 6 weeks and doxorubicin at 50 mg/m<sup>2</sup> on days 1 and 22.

Some centers use an alternative schedule: STZ 0.5 g/m<sup>2</sup> for 5 days, then repeated as a 1-day treatment 1 g/m<sup>2</sup> every 3 weeks. 5-FU is given at 400 mg/m<sup>2</sup> days 1–3 during the first course, and then 400 mg/m<sup>2</sup> every 3 weeks. When doxorubicin is combined with STZ, doxorubicin at 40 mg/m<sup>2</sup> is given on day 1 and then repeated every 3 weeks. In case of reduced creatinine clearance, the 1-day course of STZ can be given over 2 days instead.

Premedication with antiemetics, mainly serotonin-receptor blockers, should be used and prehydration with 1–2 liters of fluid is recommended to protect the kidneys.

#### Dose Adjustments

Dose adjustments may be necessary if patients develop severe nausea despite antiemetics, or if impaired renal function occurs.

**Table 1.** Dose schedules

Reference (first author)	Therapy			
Moertel 1992 [1]	STZ	0.5 g/m <sup>2</sup>	days 1–5	q 6 weeks
	DOX	50 mg/m <sup>2</sup>	days 1+22	
Moertel 1992 [1]	STZ	0.5 g/m <sup>2</sup>	days 1–5	q 6 weeks
	5-FU	400 mg/m <sup>2</sup>	days 1–5	
Eriksson 1993 [2]	STZ	0.5 g/m <sup>2</sup>	days 1–5,	q 3 weeks
		1 g/m <sup>2</sup>	then day 1	
	5-FU	400 mg/m <sup>2</sup>	days 1–3,	q 3 weeks
		400 mg/m <sup>2</sup>	then day 1	
Eriksson 1990 [3]	STZ	0.5 mg/m <sup>2</sup>	days 1–5,	q 3 weeks
		1 g/m <sup>2</sup>	then day 1	
	DOX	40 mg/m <sup>2</sup>	day 3,	q 3 weeks
			then day 1	
Moertel 1991 [4]	Etoposide	130 mg/m <sup>2</sup>	days 1–3	q 4 weeks
	Cisplatin	45 mg/m <sup>2</sup>	days 2–3	
Mitry 1999 [5]	Etoposide	100 mg/m <sup>2</sup>	days 1–3	q 4 weeks
	Cisplatin	45 mg/m <sup>2</sup>	days 2–3	
Altamari 1987 [6]	DTIC	200–250 g/m <sup>2</sup>	days 1–5	q 3–4 weeks

STZ = Streptozotocin; DOX = doxorubicin; 5-FU = fluorouracil; DTIC = dacarbazine.

#### Monitoring of Adverse Events

Check for extravasation.

Check before every course: creatinine clearance, blood counts, transaminases, bilirubin, albumin, blood glucose. EF checked every 100 mg/m<sup>2</sup> of doxorubicin.

#### Adverse Events

- Nausea – try another 5-HT<sub>3</sub>-receptor blocker or add aprepitant.
- Renal impairment – dose reductions of STZ should be considered when creatinine clearance is <60 ml/min and should not be given below 30 ml/min.
- Liver impairment – reduction of doses should be considered.
- Stomatitis – frequent mouth care.
- Cardiac toxicity – doxorubicin should be withdrawn.
- Photosensitivity – avoid direct sunlight.

At a cumulative dose of 550 mg/m<sup>2</sup> of doxorubicin, the drug must be stopped. If the patient is still responding, 5-FU may be used instead.

### *Control of Therapeutic Efficacy*

Evaluate patients every 3–6 months.

- Biochemistry:  
CgA  
Other specific markers
- Imaging:  
CT or MRI every 6 months  
US of the abdomen if indicated every 3 months.

### *Documentation and Reporting of Results*

Use RECIST or WHO criteria.

## **Combination of Cisplatin + Etoposide**

This combination should be used according to the first edition of the ENETS Guidelines. The main indication for the use of cisplatin + etoposide is treatment of poorly differentiated neuroendocrine tumors. Cisplatin has activities similar to alkylating agents and inhibits the DNA synthesis. Etoposide exerts a cytostatic effect of cells in S- and G2-phase and inhibits mitosis. It also appears to cause DNA strand breaks. The combination has been reported to produce objective responses in about 50% of anaplastic or poorly differentiated neuroendocrine tumors.

### *What Is Necessary in Preparation for Treatment with the Combination of Cisplatin + Etoposide?*

The patients should be asked about the following symptoms that might influence the decision: fever, cough, dysuria, pain or paresthesia of hands and feet, visual disturbances, headache and diarrhea. In addition, blood cell count, transaminases, bilirubin, blood glucose, serum albumin and creatinine clearance should be analyzed. Blood pressure and body weight should be checked before and during the course. For tumor disease evaluation, CgA and other elevated tumor markers should be determined and followed during treatment.

### *Patient Information*

The patient information should include description of mechanisms of action, side effects and how to react to side effects.

### *Dietary Instruction*

Against nausea, frequent small meals, sucking lozenges or chewing gum may help.

### *Drug Interactions*

The following drug interactions should be taken into consideration:

- Cyclosporine may decrease/increase the levels of etoposide.
- CYP3A4 inducers may decrease the levels of etoposide, e.g. carbamazepine, phenytoin, phenobarbital.
- CYP3A4 inhibitors may increase the levels of etoposide, e.g. clarithromycin, diclofenac, erythromycin, doxycyclin, imatinib, etc.
- Warfarin may elevate prothrombin time with concurrent use.
- Concomitant administration of nephrotoxic or ototoxic drug, e.g. aminoglycosides, should be avoided.

### *Contraindications*

#### *Pregnancy and Nursing*

- Contraceptive measures are recommended.
- Cryopreservation of sperm and ovarian tissue should be considered.

### *Initiation of Combination Therapy*

This should be given according to the ENETS Guidelines with the following schedule: etoposide at a dose of 100 mg/m<sup>2</sup> for 3 days and cisplatin at a dose of 45 mg/m<sup>2</sup> per day on days 2 and 3 by a continuous intravenous infusion in a solution of 5% dextrose and 0.45% saline. On day 1, the daily dose is given in 1,000 ml solution; on days 2 and 3, one-third of the daily dose is given in 1,000 ml solution every 8 h.

Alternative regimen: On day 1, the daily dose of etoposide (100 mg/m<sup>2</sup>) is given in 1,000 ml 5% dextrose solution. On days 2 and 3, hydration with normal saline 1,000 ml with 20 mmol potassium is given over 2 h, followed by cisplatin 45 mg/m<sup>2</sup> in 500 ml normal saline (1-hour infusion) in parallel with infusion of mannitol (150 mg/ml) 500 ml. Etoposide (100 mg/m<sup>2</sup>) is then given (2-hour infusion) in 1,000 ml glucose solution, followed by 1,000 ml of normal saline with 5 mmol magnesium and 20 mmol potassium added (2-hour infusion).

For antiemetics, the patient should receive serotonin receptor blockers on days 1–3 and dexamethasone during days 2–3 and 3 days after treatment. The diuresis should be monitored carefully during treatment and furosemide given if the diuresis is lower than 400 ml in 4 h. Extravasation should be checked for. If hypotension occurs, the etoposide infusion should be slowed down.

Courses should be repeated every 4 weeks.

### *Dose Adjustments*

- Reductions in doses of cisplatin should be made if creatinine clearance is <60 ml/min and stopped if clearance is <30 ml/min.
- Because of the high protein binding, the dose of etoposide should be reduced if albumin is <30 g/l or bilirubin >50 µmol/l or INR >1.2.

### *Monitoring of Adverse Events*

- Nausea and vomiting – aprepitant can be added if this is a problem.
- Control of serum creatinine, creatinine clearance and liver function (bilirubin, albumin, INR) should be performed before each course.
- Blood counts should be checked every week. Chemotherapy should not be repeated until leukocytes >4 × 10<sup>9</sup>/l, platelets >100 × 10<sup>9</sup>/l and hemoglobin are satisfactory.
- Audiometry should be performed before each treatment.
- Neurologic examination for peripheral neuropathy, which is dose- and duration-dependent.
- Anaphylactic-like reactions should be looked for.

### *Adverse Effects*

- Alopecia – reversible.
- Nausea and vomiting – 5-HT<sub>3</sub> blockers, dexamethasone and aprepitant should be used.
- Hypotension – slow the infusion of etoposide.
- Nephrotoxicity; prehydration and maintained diuresis important, furosemide may be used if necessary; body weight should be checked.
- Susceptibility to infections – patients should avoid crowds.
- Avoid alcohol and aspirin-containing products.
- Diarrhea – eat yoghurt or buttermilk.
- Stomatitis – frequent mouth care.

### *Control of Therapeutic Efficacy*

Evaluate patients every 2–3 months.

- Biochemistry:  
CgA  
Other elevated tumor marker
- Imaging:  
CT or MR every 2–3 months.

### *Documentation*

Use the RECIST or WHO criteria.

## **Treatment with Dacarbazine**

Some early publications reported beneficial effects of dacarbazine (DTIC) treatment in patients with malignant abdominal tumors. The main indication could be malignant neuroendocrine pancreatic tumors, when biotherapy and combinations with STZ have failed. DTIC is an alkylating agent that causes cross-links of DNA resulting in the inhibition of DNA, RNA, and protein synthesis. The drug may induce tumor responses in patients with neuroendocrine tumors.

### *What Is Necessary in Preparation for Treatment with DTIC?*

The patients should be asked about the presence of fever, cough, dysuria, headache and diarrhea. Basal investigations include blood cell count, transaminases, bilirubin, albumin, blood glucose and creatinine clearance. Blood pressure and body weight should be checked. Biochemical tumor markers, including CgA, should be determined before and followed during treatment.

### *Patient Information*

The patient information should include description of mechanisms of action, side effects and how to react to side effects.

### *Drug Interactions*

Since DTIC is extensively metabolized in the liver, it interacts with a number of other drugs.

- CYP1A2 inducers may decrease levels/effects of DTIC; examples carbamazepine, phenobarbital.
- CYP1A2 inhibitors may increase levels/effects of DTIC; examples ciprofloxacin, ketoconazole, etc.
- CYP2E1 inhibitors may increase levels/effects of the drug; examples disulfiram, miconazole.
- Vaccines, live virus may cause viral infections in patients receiving DTIC.

### *Dietary Considerations*

Patients should limit oral intake for 4–6 h before therapy. They should not use alcohol or aspirin-containing products and should maintain adequate nutrition and hydration during therapy.

### *Contraindications*

#### *Pregnancy and Nursing*

- Contraceptive measures are strongly recommended.

- Cryopreservation of sperm and ovarian tissue should be considered.

#### *Initiation of Treatment with DTIC*

Different schedules have been used. The most commonly used are:

- intravenous infusion of 650 mg/m<sup>2</sup> over 60–90 min, repeated every 4 weeks  
or
- intravenous infusion of 200–250 mg/m<sup>2</sup> over 30–60 min repeated every 3 weeks.

DTIC may cause tissue damage. If this occurs, a central line should be used.

#### *Dose Adjustments*

- Renal impairment requires dose adjustments.
- Hepatic impairment should be looked for (and the extremely rare adverse event of liver necrosis due to occlusion of intrahepatic veins).
- Myelosuppression may be severe and lead to postponement or withdrawal of treatment.
- Nausea and vomiting are very common and can be dose-limiting.

#### *Monitoring of Adverse Events*

- Blood cell count every week.
- Liver function before each course (bilirubin, albumin, transaminases).
- Creatinine clearance before each course.

#### *Adverse Events*

- Alopecia – reversible.
- Nausea and vomiting – 5-HT<sub>3</sub>-receptor blocker, dexamethasone and aprepitant should be used.
- Myelosuppression for neutropenia filgrastim may be used.
- To avoid pain on infusion, a central line should be used.
- Photosensitivity – patients should avoid direct exposure to sunlight.
- Flu-like syndrome – could last for a week.
- Anaphylactic reactions and hepatic necrosis occur in <1% of patients.

#### *Control of Therapeutic Efficacy*

Evaluate patients every 2–3 months.

- Biochemistry:  
CgA  
Other tumor markers

- Imaging:  
CT or MRI every 2–3 months.

#### *Documentation*

Use the RECIST or WHO criteria.

### **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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