



ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Chemotherapy

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ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms. Systemic Therapy 2: Chemotherapy

Rocio Garcia-Carbonero¹, Anja Rinke², Juan W. Valle³, Nicola Fazio⁴, Martyn Caplin⁵, Vera Gorbounova⁶, Juan O'Connor⁷, Barbro Eriksson⁸, Halfdan Sorbye⁹, Mathew Kulke¹⁰, Jie Chen¹¹, Jenny Falkerby⁸, Frederico Costa¹², Wouter de Herder¹³, Catherine Lombard-Bohas¹⁴, Marianne Pavel¹⁵; all other Antibes Consensus Conference participants*

1. Medical Oncology Department, Hospital Universitario Doce de Octubre, Madrid, Spain
2. Division of Gastroenterology and Endocrinology, University Hospital Marburg (UKGM), Marburg, Germany
3. Department of Medical Oncology, University of Manchester, Institute of Cancer Sciences / The Christie NHS Foundation Trust, Manchester, United Kingdom
4. Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy
5. Neuroendocrine Tumour Unit, Royal Free Hospital, London, United Kingdom
6. Department of Oncology, Institution of Russian Academy of Medical Sciences, Moscow, Russia
7. Department of Clinical Oncology, Institute Alexander Fleming, Buenos Aires, Argentina
8. Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden
9. Department of Oncology, Haukeland University Hospital, Bergen, Norway
10. Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA
11. Department of Gastroenterology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
12. Hospital Sirio Libanes, Sao Paulo, Brazil
13. Department of Internal Medicine, Division of Endocrinology, ENETS Centre of Excellence Rotterdam, Erasmus MC, Rotterdam, the Netherlands
14. Medical Oncology Department, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France
15. Department of Hepatology and Gastroenterology, Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany

* For an alphabetical list of all other Antibes Consensus Conference participants, see Appendix

Corresponding author:

Rocio Garcia-Carbonero
Medical Oncology Department
Hospital Universitario Doce de Octubre.
Avenida de Córdoba, s/n, 28041 Madrid, Spain
Phone: +34 91 3908926
Fax: +34 91 4603310
Email: rgcarbonero@gmail.com

Abstract

Systemic chemotherapy is indicated in progressive or bulky advanced pancreatic neuroendocrine tumors (NETs) and in grade 3 (G3) neuroendocrine neoplasms (NENs) as per ENETS Guidelines. Chemotherapy may be considered in NETs of other sites (lung, thymus, stomach, colon, rectum) under certain conditions (e.g., when Ki-67 is at a high level (upper G2 range), in rapidly progressive disease and/or after failure of other therapies, or if somatostatin receptor imaging is negative). An ENETS

Consensus Conference was held in Antibes (2015) to elaborate guidelines on the standards of care of different diagnostic procedures and therapeutic interventions in NENs. This article provides guidance on chemotherapy including therapeutic indications, dosing schedules, adverse events (including prevention and management), drug interactions and evaluation of treatment effect for the chemotherapy agents most commonly used in NENs (streptozocin, dacarbazine, streptozocin, fluoropyrimidines, platinum compounds, etoposide and irinotecan).

Introduction

Systemic therapies that are established as standards of care (SOCs) for neuroendocrine neoplasms (NENs) include somatostatin analogues (SSA), alpha interferon (IFN), novel targeted agents (everolimus, sunitinib), and chemotherapy. Other novel targeted agents (e.g. bevacizumab, axitinib, pazopanib) have been recently investigated in phase II trials in neuroendocrine tumors (NETs), but are not currently approved for the management of NETs and thus will not be covered by these guidelines. SOCs for SSA, IFN and targeted therapy will be covered in a separate chapter. The current manuscript will cover SOCs related to chemotherapy.

Indication

Systemic chemotherapy is indicated in progressive or bulky advanced pancreatic NETs and in grade 3 (G3) NENs as per ENETS Guidelines [1,2]. Chemotherapy may be considered in NETs of other sites (lung, thymus, stomach, colon, rectum) under certain conditions (e.g., when Ki-67 is at a high level (upper G2 range), in rapidly progressive disease and/or after failure of other therapies, or if somatostatin receptor imaging is negative) [1,2].

Streptozocin (STZ)-based chemotherapy is one of the treatment options in G1/G2 pancreatic NET, and is preferably recommended in patients with higher tumor burden, with or without associated clinical symptoms, and/or in patients with significant tumor progression within a 6 to 12 months time frame [3-6]. The combination of STZ with doxorubicin proved to be more effective than STZ with 5-fluorouracil (5FU) in the pivotal randomized study by Moertel [5]. However, the use of doxorubicin is limited by its cumulative cardiotoxicity. Chemotherapeutic options after failure of STZ-based chemotherapy include the following: temozolomide (TMZ) +/- capecitabine [7-12], dacarbazine [13-15], oxaliplatin combinations with fluoropyrimidines (5-FU or capecitabine) [16,17] and irinotecan-based therapy [18]. Although data for TMZ-based chemotherapy are still limited, it may replace STZ-based therapy in pancreatic NEN, if STZ is not available, and may be considered in NET G3 and in high risk NET of other primary sites (e.g., pulmonary NET) [19-21].

In high grade neuroendocrine carcinomas (NEC G3), chemotherapy is an essential part of the multimodality approach for localized disease and the mainstay of care in advanced or metastatic disease [1]. Platinum-based chemotherapy is generally indicated provided the patient has adequate organ function and performance status [22-24]. The combination of cisplatin and etoposide, or alternative regimens substituting carboplatin for cisplatin, or irinotecan for etoposide, are recommended as first-line therapy [25-28]. Since response rates of these regimens are lower in patients with Ki-67 in the lower range of G3 (21-55%), other treatment options may be explored in these patients (particularly for G3 NEN of GI origin), although no studies to date have demonstrated improved efficacy of these alternative regimens in this setting. While 2nd-line regimens have not been evaluated rigorously, options include temozolomide-, irinotecan- or oxaliplatin-based schedules as main alternatives [1]. Efficacy of chemotherapy in NET G3 is presently uncertain.

Dosing Schedules: Drug disposition, posology and mode of administration

The most widely used chemotherapy regimens or those supported by more solid evidence in gastroenteropancreatic NENs are depicted in Tables 1, 2 & 3. The pharmaceutical presentation, drug disposition, route and mode of administration of the most commonly employed cytotoxic agents are briefly summarized below.

Doxorubicin (DOX)

Doxorubicin is administered IV by rapid infusion (2-3 minutes). It does not cross the blood-brain barrier, but does cross the placenta and is distributed into breast milk. Doxorubicin undergoes rapid metabolism in the liver. Dose should be adjusted in case of liver impairment (50% reduction for bilirubin levels of 1.2-3 mg/dl; a 75% dose reduction is advised in obese patients and if bilirubin levels are > 3 mg/dl, although it is not generally recommended to treat NEN patients with this degree of liver dysfunction). Doses do not need to be adjusted for renal function impairment unless severely compromised (25% dose reduction is advised if glomerular filtration rate (GFR) < 10 ml/min, although it may be more appropriate not to treat patients with this degree of renal dysfunction) [29,30].

Streptozocin (STZ)

Streptozocin is administered IV by rapid injection or short (15-30 minutes) infusion. A single dose of 1500 mg/m² should not be exceeded due to high risk of nephrotoxicity. Metabolism and drug disposition of streptozocin has been barely studied in humans, but in animal studies up to 20% of the drug is excreted by the kidney [29,31]. STZ should thus be used with caution in patients with preexisting renal disease as it may increase the risk of drug exposure and drug-related toxicity including renal damage.

Dacarbazine

Dacarbazine may be administered by IV bolus injection or as a short-term infusion (15 –30 minutes). Dacarbazine is inactive until metabolised by cytochrome P450 (CYP450) to form the reactive N-demethylated species HMMTIC and MTIC. Dacarbazine is metabolized mainly in the liver and 20–50 % of the drug is excreted unmodified by the kidney. Dose reductions are not required in patients with mild to moderate renal or hepatic insufficiency. Elimination of dacarbazine is prolonged, however, in patients with combined renal and hepatic dysfunction, and it should therefore be used with caution in this context [29,32].

Temozolomide (TMZ)

TMZ is administered orally as hard capsules of 5 mg, 20 mg, 100 mg, 140 mg, 180 mg or 250 mg. The capsules shall be administered in a fasting state and must not be opened or chewed. If vomiting occurs following drug ingestion, a second dose should not be administered that day.

TMZ is spontaneously hydrolyzed to the active species, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC). MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) and to methylhydrazine, which is believed to be the active alkylating species. TMZ cytotoxicity is thought to be primarily due to alkylation of DNA at the O6 and N7 positions of guanine [33].

TMZ is rapidly absorbed and crosses the blood-brain barrier. The major route of TMZ elimination is renal. TMZ plasma clearance is independent of age, renal or liver function. However, caution should be exercised when TMZ is administered in patients with severe liver or renal function impairment, as available data are very limited in these populations [29,34].

5-Fluorouracil (5-FU)

5-FU is administered IV by rapid injection or short infusion, and may also be given as a continuous IV infusion over 24-48 hours (or even longer) through a portable pump. Following a single IV injection approximately 15% of the dose is excreted unchanged in the urine within 6 hours. The remainder is mostly metabolised in the liver. 5-FU readily enters the cerebrospinal fluid and brain tissue. Dose adjustments are recommended in patients with poor nutritional status, impaired hepatic or renal function, or limited bone marrow reserve (e.g. extensive prior irradiation) [35,36].

Capecitabine (CAP)

Capecitabine is an oral fluoropyrimidine rationally designed to generate 5-FU preferentially in tumour tissue. After oral administration it is rapidly absorbed, and extensively metabolised in the liver and tumor tissues to 5-FU via a three-step enzymatic cascade [37]. Dihydropyrimidine dehydrogenase (DPD) activity is the rate-limiting step in 5-FU catabolism. Deficiency of DPD may lead to increased toxicity of capecitabine and 5-FU. No dose has proven to be safe for patients with complete absence of DPD activity. For patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene), and where the benefits of capecitabine are considered to outweigh the risks, capecitabine may be given with extreme caution and frequent monitoring with dose adjustment according to toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by a specific test [38,39].

Capecitabine is administered orally as film-coated tablets of 150 mg and 500 mg. Tablets should be swallowed with water within 30 minutes after a meal. It is predominantly excreted in urine (96% of administered dose), with minimal faecal excretion (<3%). Capecitabine is contraindicated in patients with severe renal dysfunction (creatinine clearance (CrCl) < 30 ml/min). In patients with moderate renal impairment, a dose reduction to 75% for a starting dose of 1250 mg/m² is recommended (no dose reduction required for a starting dose of 1000 mg/m²). In patients with mild renal impairment (CrCl of 51-80 ml/min) no dose adjustment is needed. Insufficient data are available in patients with hepatic impairment to provide dose adjustment recommendations. No dose adjustment is recommended for elderly patients although they should be monitored more carefully as their risk of severe toxicity is greater [29,37].

Cisplatin (Cis-Diamine-Dichloro-Platinum, CDDP)

Cisplatin is usually administered by IV infusion over 1 to 2 hours (a longer infusion time of 6 to 8 hours may decrease gastrointestinal and renal toxicities). Intensive pre- and posttreatment IV hydration (3-4 litres of saline solution over a minimum of 6 hours for doses above 50 mg/m², together with magnesium and potassium supplementation) is required to force diuresis and prevent renal toxicity. If vigorous hydration is insufficient to maintain an adequate urinary output (≥ 100 ml/hour recommended), an osmotic diuretic may be administered (e.g. mannitol). Cisplatin may interact with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should therefore be avoided [29,40].

There is good uptake of cisplatin by the kidneys, liver and intestine. Penetration into the cerebrospinal fluid is poor although significant amounts of cisplatin can be detected in intracerebral tumours. The elimination of intact drug and metabolites occurs primarily through the urine (20-80% during the first 24 hours). Use is therefore contraindicated in patients with pre-existing renal impairment and also in patients with a history of allergic reaction to other platinum compounds. Dose adjustments are not required in patients with liver dysfunction [29,40]

Carboplatin (CycloButane DiCarboxylic Acid, CBDCA)

Carboplatin is usually administered as a 1 hour IV infusion. Aluminium-containing equipment should not be used. Carboplatin is excreted primarily in urine, with recovery of 65% of administered dose within 24 hours. Patients with CrCl < 60 ml/min are therefore at increased risk of severe myelosuppression. Nevertheless, the Calvert formula permits to determine carboplatin dosage adjusted to renal function: Dose (mg) = target AUC (mg/ml x min) x [GFR ml/min + 25]. Insufficient data exist, however, on the use of carboplatin in patients with CrCl ≤ 15 ml/min to permit a recommendation for treatment [29,40,41].

Oxaliplatin (OX)

Oxaliplatin is administered as a 2 to 6-hour IV infusion, and must always precede the administration of 5-fluorouracil. It does not require hyperhydration. Platinum is predominantly excreted in urine [42,43]. No dose adjustments are required in patients with mild renal impairment. Those with moderate renal impairment, treatment may be initiated at standard doses but toxicities and renal function should be closely monitored. Oxaliplatin has not been studied in patients with severe renal dysfunction. No specific dose adjustment is required for patients with abnormal liver function tests nor for elderly patients [29,43].

Etoposide (VP-16)

Etoposide is generally given by IV injection (30-60 minutes) although it is also available as soft capsules of 50 mg and 100 mg for oral intake. Hypotension after rapid IV administration has been reported, so longer infusion times may be required depending on patient's tolerance. If etoposide injection comes into contact with skin or mucosa, immediately wash thoroughly with soap and water. The capsules should be taken on an empty stomach [43, 44].

Etoposide has relatively poor penetration into the cerebrospinal fluid. Following IV administration, 42-67% of the dose is recovered in urine and 0-16% in faeces. Impaired hepatic or renal function may increase etoposide concentration in tissues. Dose should be reduced to 75% in patients with CrCl of 15-50 mL/min. Data are not available in patients with CrCl <15 mL/min and further dose reductions or alternative treatment options should be considered in these patients. No specific dosing guidelines exist for patients with impaired liver function [46].

Irinotecan (CPT-11)

Irinotecan is administered by IV infusion over 30 to 90 minutes. Irinotecan is metabolized by a carboxylesterase (present in intestinal mucosa, plasma and liver) into a highly active metabolite, SN-38, which is further converted to inactive glucuronide (SN-38G) by UGT1A (uridine diphosphate glucuronosyltransferase). 55% of administered dose is excreted as unchanged drug (33% in faeces and 22% in urine) [47,48].

In patients with bilirubinemia of 1.5 to 3 times above the upper limit of normal (ULN), irinotecan clearance decreases by about 40% and dose should be adjusted accordingly. Irinotecan should not be given to patients with plasma bilirubin > 3 xULN. Its use is also contraindicated in patients with chronic inflammatory bowel disease and/or bowel obstruction. No specific dosing recommendations are provided for patients with renal impairment nor for elderly patients [49,50].

Adverse events (AEs)

The most common side effects of the individual cytotoxic agents are summarized below. For more comprehensive information regarding potential AEs the reader is referred to the summary of product characteristics (SPCs) of each individual drug elaborated by marketing authorization holders (MAH) following regulatory agencies' requirements. It should also be noted that additive effects may occur when several of these drugs are combined in a given treatment regimen. Reported rates of adverse events of most commonly used chemotherapy regimens in NENs are summarized in Table 4 (data are derived from clinical trials in NENs when available, or from detailed reports of retrospective NEN series or clinical trials conducted in GI cancer in the absence of disease-specific clinical trials).

Doxorubicin

Common side effects include myelosuppression (anemia, leucopenia, thrombocytopenia), nausea and vomiting (moderately emetogenic), mucositis, anorexia, diarrhea, cardiotoxicity (tachyarrhythmia, bradycardia, bundle branch block, decrease of left ventricular ejection fraction (LVEF), congestive heart failure), and alopecia. Doxorubicin is a potent, radiosensitizing agent, and recall phenomena may occur. Caution is advised to prevent extravasation as it can lead to severe cellulitis and vesication [49].

In order to avoid cardiomyopathy, the cumulative total lifetime dose of doxorubicin should not exceed 450-550 mg/m² body surface area. In patients with cardiac risk factors such as prior thoracic irradiation, prior or concurrent treatment with potentially cardiotoxic agents, chronic hypertension, prior coronary, valvular or myocardial heart damage, age over 70 years or children, the total cumulative dose should not exceed 400 mg/m² and cardiac function should be closely monitored in these patients [29,50].

Streptozocin

Renal toxicity of streptozocin includes proteinuria, hypophosphatemia, azotemia and renal tubular acidosis. Mild proteinuria is one of the first signs of renal toxicity and may herald further deterioration of renal function. Although generally mild, renal toxicity is dose-related and cumulative, and severe cases have been reported. Adequate hydration may help reduce the risk of nephrotoxicity. Other major toxicities are nausea and vomiting, which may be severe if appropriate antiemetic prophylaxis is not implemented. In addition, mild to moderate abnormalities of glucose tolerance, liver dysfunction (elevated liver enzymes, hypoalbuminemia), diarrhea, and hematological toxicity have been observed in some patients. Extravasation may cause severe tissue lesions and necrosis. Streptozocin is mutagenic and carcinogenic [29,31].

Dacarbazine

The most common side effects of dacarbazine (occurring in > 10% of treated patients) include nausea and vomiting (highly emetogenic), injection site pain and delayed myelosuppression (cumulative, dose dependent). Other less common AEs (occurring in 1-10% of patients) are alopecia, anorexia, taste disturbances (metallic taste), flu-like syndrome, photosensitivity and rash. Liver and renal toxicities are rare [29,32].

Temozolomide

Very common adverse reactions include mild nausea, vomiting, constipation, anorexia, rash, headache

and fatigue. Convulsions were commonly reported in patients receiving TMZ as monotherapy or concurrent with RT for glioblastoma or glioma, although they have not been reported in other non-CNS tumors. Haematologic toxicity is common although generally mild (grade ≥ 3 anemia, leucopenia and thrombocytopenia: 3%, 3% and 14% when used as monotherapy). However, the incidence of grade 3-4 lymphopenia has been observed in over 40% of patients after 4 months of therapy and may remain in $> 30\%$ for 12 months following treatment discontinuation. The overall incidence of opportunistic infections is 10% (up to 20% in patients receiving more than 7 months of treatment). Prophylaxis for *Pneumocystis jiroveci* pneumonia and varicella-zoster, as well as cytomegalovirus shall be considered in patients with prolonged TMZ treatment. Liver enzymes elevations are common and cases of hepatic failure have been reported. Liver toxicity may occur several weeks after TMZ administration. Liver function tests should therefore be performed prior to each treatment cycle and several weeks after treatment discontinuation. TMZ should not be used in patients with hypersensitivity to dacarbazine [29,34].

5-Fluorouracil

Common side effects of 5-FU include myelosuppression (leucopenia, thrombocytopenia, pancytopenia), diarrhea, nausea and vomiting, anorexia, asthenia, mucositis, and palmar-plantar erythrodysesthesia syndrome (dysaesthesia of the palms and soles that progress to pain and tenderness, with associated symmetrical swelling and erythema of the hand and foot; more common with protracted infusion or oral fluoropyrimidines). Alopecia is not uncommon, particularly in females, but is reversible. Electrocardiographic changes (exceptionally including QT prolongation), angina pectoris-like chest pain and rarely myocardial infarction have been also associated with 5-FU therapy, and are attributed to drug-induced vasospasm. Special attention is advisable in patients with a history of heart disease or severe atheromatosis, and in those who experience chest pain during treatment courses. Central nervous system toxicity (dizziness, pyramidal signs, ataxia and somnolence) is uncommon. Severe or even lethal toxicity may occur in patients with DPD deficiency (3-5% of the population) [29,51].

Capecitabine

Capecitabine's toxicity profile is very similar to that of 5-FU, but it is associated with less hematological toxicity and a greater incidence of hand-foot syndrome and liver toxicity (most commonly hyperbilirubinemia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. Caution is advised in patients with a history of heart disease or DPD deficiency [29,52].

Cisplatin

The most frequently reported AEs of cisplatin (occurring in $>10\%$ of patients) are hematological (leukopenia, thrombocytopenia and anemia), gastrointestinal (anorexia, nausea, vomiting and diarrhea), ear disorders (hearing impairment), renal disorders (renal failure, hyperuricaemia) and fever. Peripheral sensory neurotoxicity is also common, and varies from paresthesia in fingers to ataxic gait, which might be transient or irreversible. Neurological, renal, bone marrow and ear toxicity are generally dose-related and cumulative. Ototoxicity may be more severe in children. Intense hydration is essential to prevent nephrotoxicity. Allergic reactions may occur. Cross reactions have been reported with all platinum compounds [29,53,54].

Carboplatin

The toxicity profile of carboplatin is similar to that of cisplatin, but it is moderately emetogenic (in contrast to cisplatin that is highly emetogenic) and it is associated with less nephrotoxicity, ototoxicity and neurotoxicity. Myelosuppression is the dose-limiting toxicity of carboplatin. At very high dosages severe liver toxicity has been reported [29,53].

Oxaliplatin

Oxaliplatin is almost universally administered in combination with fluoropyrimidines, increasing the incidence and severity of gastrointestinal (diarrhea, nausea, vomiting and mucositis), hematological (neutropenia, thrombocytopenia) and neurological toxicity induced by fluoropyrimidines when administered alone.

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities often triggered by cold. These symptoms occur in up to 95% of treated patients, are dose-related and cumulative, and generally improve or revert upon treatment discontinuation. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1-2% of patients, and is characterised by subjective sensations of dysphagia or dyspnoea, without any objective evidence of respiratory distress (no cyanosis or hypoxia, no stridor or wheezing). These symptoms are rapidly reversible upon infusion discontinuation even in the absence of treatment (no need for antihistamines, corticoids or bronchodilators), and should be distinguished from hypersensitivity reactions. Other less common side effects include muscle spasms (often jaw spasms), balance disorders, throat or chest pressure/discomfort/pain, and cranial nerve dysfunctions (ptosis, diplopia, dysphonia, abnormal tongue sensation or dysarthria, visual disorders) [53,55].

Etoposide

The dose-limiting effect of etoposide is myelosuppression. Nausea and vomiting are also common (they occur in 31–43% of patients). Other gastrointestinal toxicities include anorexia (10–13%), stomatitis (1–6%) and diarrhea (1-13%). Reversible alopecia has been observed in about 2/3 of patients. Transient hypotension may occur following rapid IV administration. Anaphylactic type reactions have been reported to occur during or immediately after IV administration of etoposide. Caution is advised in patients with low serum albumin levels and those with impaired renal or liver function due to increased risk of toxicity. Etoposide is mutagenic and carcinogenic [29].

Irinotecan

The most frequent dose-limiting toxicities of irinotecan include hematological toxicity (neutropenia, anemia and thrombocytopenia) and delayed diarrhea (occurring more than 24 hours after drug administration). The concurrent occurrence of neutropenia and diarrhea confers a particular risk of severe infections. Irinotecan also commonly induces a transient acute cholinergic syndrome, which is characterized by early diarrhea, abdominal cramps, vasodilatation, sweating, dizziness, visual disturbances, miosis, lacrimation and increased salivation occurring during or within the first 24 hours after drug infusion. This syndrome is generally easily controlled with subcutaneous atropine administration (0.25 mg). Other side effects include alopecia, and transient and mild to moderate increases in serum levels of alanine transferase (ALT), aspartate transaminase (AST), alkaline

phosphatase or bilirubin. Liver toxicity is more commonly observed when irinotecan is administered in combination with other drugs such as fluoropyrimidines [48].

The main active metabolite, SN-38, is detoxified by UGT1A1 to SN-38 glucuronide. Individuals with a congenital UGT1A1 deficiency (Crigler-Najjar or Gilbert's syndrome) are at increased risk of irinotecan toxicity. A reduced initial dose should be considered for these patients [47].

Of note, as irinotecan solution contains sorbitol (excipient), it is not suitable for patients with fructose intolerance.

Prevention, management and dose adjustments for AEs

Prevention of adverse events

Antiemetic prophylaxis should be prescribed following ASCO, NCCN or MASCC-ESMO guidelines. For highly emetogenic agents (e.g. cisplatin, dacarbazine, streptozocin), a 3-drug combination of a neurokinin 1 antagonist (aprepitant, fosaprepitant, netupitant), a 5-hydroxytryptamine-3 antagonist (granisetron, ondansetron, palonosetron, dolasetron, tropisetron, ramosetron) and dexamethasone should be offered. For agents with a moderate emetic risk (e.g. oxaliplatin, carboplatin, doxorubicin, irinotecan, temozolomide), prophylaxis with 5-hydroxytryptamine-3 antagonists and dexamethasone is recommended. Prophylaxis with corticosteroids alone is advised for low emetogenic drugs (e.g. 5-FU) [56,57].

Primary febrile neutropenia (FN) prophylaxis with granulocyte colony-stimulating factors (G-CSF) is not generally indicated for chemotherapy regimens usually employed in the treatment of NENs (risk of FN < 20%). Secondary prophylaxis should follow ASCO guidelines [58].

Doxorubicin-induced cardiac toxicity may be prevented by limiting the cumulative total lifetime dose to 450-550 mg/m² (400 mg/m² in patients with cardiac risk factors). Cardiac function (LVEF) should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy, particularly with higher cumulative doses. Treatment should be discontinued in case significant cardiac function deterioration is documented [49,50].

Cisplatin-induced renal toxicity may be prevented by intense hydration prior and after drug administration by decreasing renal and urinary concentration of the drug and its metabolites [54]. Adequate hydration is also important to reduce the risk of streptozocin-induced renal toxicity. Carboplatin dose should be adjusted to glomerular filtration rate.

Oxaliplatin-induced acute laryngopharyngeal dysaesthesia and sensory peripheral neuropathy may be minimized by avoiding cold exposure and by increasing drug infusion time. If functional impairment persists until the next cycle, treatment with oxaliplatin should be delayed or discontinued [55].

Fluoropyrimidines should not be given to patients with known complete absence of DPD activity. Patients with partial DPD deficiency must be treated with extreme caution and frequent monitoring with dose adjustments according to toxicity [39].

Chemotherapy should be given with caution to high risk patients who have recently undergone surgery, have a history of high-dose irradiation of bone marrow-bearing areas (pelvis, spine, ribs, etc.), have received prior myelosuppressive chemotherapeutic agents or peptide-receptor radionuclide therapy (PRRT), have a widespread involvement of bone marrow by metastatic tumours, have reduced renal or liver function, or a poor nutritional state.

Treatment cycles with myelosuppressive drugs should not begin if the neutrophil count is less than 1,500 cells/mm³ or the platelet count is less than 100,000 cells/mm³, unless caused by malignant

disease.

More frequent INR monitoring or a switch to subcutaneous heparine is recommended for patients on oral anticoagulants due to potential interactions between oral anticoagulants and many antineoplastic agents.

Viral hepatitis due to hepatitis B or C virus (HBV/HCV) reactivation may occur during chemotherapy. Baseline serologies are recommended in all patients and experts in liver disease should be consulted if positive for adequate monitorization and management. Antiviral therapy should be started for HBsAg-positive/anti-HBc-positive patients before or concurrently with cancer therapy. Antivirals may be initiated in HBsAg-negative/anti-HBc-positive patients if they are to receive cancer therapies associated with a high risk of reactivation; alternatively, they may be monitored with HBV DNA and ALT levels and initiate on-demand antivirals if reactivation occurs. [59].

Live attenuated vaccines should be avoided but inactivated vaccines may be used.

Patients should be informed that there may be a potential risk in driving or using complex machinery after chemotherapy administration due to confusion or lethargy.

Management and dose adjustments for most common AEs

Nausea and vomiting. The development of new antiemetic agents and prophylaxis regimens has dramatically reduced chemotherapy-induced emesis. If nausea and vomiting develop despite adequate adherence to prophylaxis guidelines, symptomatic and supportive measures (oral or parenteral) shall be administered to prevent dehydration, and intensification of antiemetic prophylaxis shall be implemented in subsequent cycles. No chemotherapy dose adjustments are generally required.

Mucositis. Adequate oral hygiene and dental care is advised prior to initiation of therapy. Treatment of mucositis relies on symptom management and prevention of complications, which includes pain control, fluid and nutritional support, and prophylaxis/treatment of secondary infections. In mild cases, pain can be controlled with locally applied products containing mucosal coating agents and lidocaine or doxepin. In severe or persistent cases, treatment with local or systemic corticosteroids and oral or parenteral analgesics may be considered. Secondary candidiasis is a common complication that is generally treated with topical antifungal therapy. In patients that develop grade ≥ 2 mucositis, chemotherapy should be interrupted and next cycle of therapy delayed until mucositis recovers to grade ≤ 1 . Dose should be reduced in subsequent cycles by 20-30% in patients that develop grade 3-4 mucositis.

Diarrhea. Early intervention is advised to prevent complications such as dehydration and electrolyte disturbances. General measures include an astringent diet, oral rehydration with fluids that contain water, salt, and sugar, and intensive loperamide therapy. Somatostatin analogues and opium derivatives may be employed in severe or refractory cases. In patients that develop chemotherapy-induced grade ≥ 2 diarrhea (to be distinguished from hormone-related diarrhea in functioning NETs), chemotherapy should be interrupted and next cycle of therapy delayed until diarrhea recovers to grade ≤ 1 . Dose should be reduced in subsequent cycles by 20-30% in patients that develop grade 3-4 diarrhea.

Hand-foot syndrome. Supportive measures include frequent hydrating, emollient and keratolytic creams (e.g. 10% urea cream), high-potency topical corticosteroids, wound care for erosions and ulcerations to prevent infection, and pain control. Treatment interruption is advised in patients that develop grade ≥ 2 hand-foot syndrome, with symptoms typically improving within 1 to 2 weeks. Treatment may be reinitiated once it recovers to grade ≤ 1 , generally at reduced doses.

Hematological toxicity. Supportive measures including blood and platelet transfusions may be indicated in severe cases. Chemotherapy should be interrupted in case of grade ≥ 2 toxicity, and next cycle delayed until recovery to grade ≤ 1 . Dose in subsequent cycles should be reduced in case of grade 3-4 toxicity.

Neutropenic fever. Early intervention with empiric broad spectrum antibiotics is recommended even in the absence of clinical or microbiological documentation of infection. Specific antibiotic, antifungal or antiviral agents and adequate supportive measures shall be instituted as needed. G-CSF therapy may be considered in high risk patients or severe episodes. Chemotherapy should be interrupted and next cycle delayed until complete resolution of the episode and neutrophil count recovery to grade ≤ 1 . Dose should be reduced by 20-30% and/or G-CSF support shall be considered in subsequent cycles.

Renal or liver toxicity. Management includes avoidance of hepato- or nephrotoxic drugs, supportive measures and symptomatic therapy. Chemotherapy should be interrupted in case of grade ≥ 2 toxicity, and next cycle delayed until recovery to grade ≤ 1 or to baseline analytical levels. Dose reductions should be considered in subsequent cycles.

Neurotoxicity. Although several neuroprotective agents have been tested (e.g., calcium/magnesium, vitamin E, glutathione, amifostine, xaliproden, or venlafaxine), no solid evidence supports their use for the prevention or treatment of platinum-induced neuropathy in routine clinical practice. Chemotherapy should be interrupted in case of persistent grade ≥ 2 toxicity, and next cycle delayed until recovery to grade ≤ 1 . Dose in subsequent cycles should be reduced by 20-30% in case of grade 3-4 toxicity. Appropriate analgesics for neuropathic pain may be required.

Drug extravasation. The degree of damage is dependent on the type of drug, drug concentration, extravasation site and duration of tissue exposure to drug damage. Extravasated drugs are classified according to their potential for causing damage as 'vesicant' (e.g. doxorubicin), 'irritant' (e.g. streptozocin, dacarbazine, etoposide, fluorouracil, platinum compounds, irinotecan) and 'nonvesicant' (e.g. monoclonal antibodies) [60]. Extravasated anthracyclines, antibiotics and alkylating agents should be localized (apply dry cold compresses for 20 minutes 4 times daily for 1-2 days) and neutralized with specific antidotes (e.g. topical dimethyl sulfoxide (DMSO) and dexrazosane for anthracyclines). Extravasated taxanes, vinca alkaloids and platinum salts should be dispersed (apply dry warm compresses for 20 minutes 4 times daily for 1-2 days) and diluted (administer agents increasing resorption such as hyaluronidase for vinca alkaloids and taxanes). Local injection of dexamethasone or hydrocortisone may be administered to minimise tissue necrosis. Oral analgesics or anti-inflammatory agents may also be used. Surgical debridement may be necessary in severe cases.

Monitoring of adverse events

Patients should be regularly followed during chemotherapy every 2 to 6 weeks (depending on treatment schedule). Toxicity should be graded according to the universal Common Terminology Criteria for Adverse Events (CTCAE) (latest update v5.0, currently under review) [61].

Before starting chemotherapy the following investigations are recommended:

- Thorough physical exam and assessment of clinical condition and comorbidities. Baseline performance status (PS), body weight, height and blood pressure should be recorded.
- Review of concomitant medication and assessment of potential drug interactions.
- Laboratory: blood cell count, glucose, electrolytes, renal and liver function tests.
- Hepatitis B and C virus screening.
- ECG and LVEF for potentially cardiotoxic drugs.

During chemotherapy the following monitoring investigations are recommended:

- Assessment of clinical condition, PS and body weight at least every 4-6 weeks.
- Blood cell count, glucose, electrolytes, renal and liver function tests prior to each treatment cycle (more often if clinically required).
- Routine viral monitoring and treatment when indicated in patients with a history of, or at high risk of, HCV or HBV.
- Monitoring of cardiac function (ECG and echocardiography or MUGA scan) every 2-3 months for potentially cardiotoxic drugs (more often if clinically indicated).

Evaluation of treatment effect

Biochemical response

Before starting chemotherapy the following biomarkers should be measured:

- Chromogranin A (CgA) or Neuron-specific Enolase (NSE) if CgA within normal limits and/or in poorly differentiated neuroendocrine carcinomas.
- 5-hydroxy-indolacetic acid (5-HIAA) urine excretion in 24 hours (collect urine on acetic acid or hydrochloric acid following local laboratory procedures) or in blood (serum or plasma) in patients with possible or definitive carcinoid syndrome.
- Additional tumor markers depending on tumor type only if clinically indicated (i.e gastrin, VIP, glucagon, insulin,..).

During chemotherapy assessment of the following biomarkers are recommended:

- Elevated tumor markers on baseline assessment should be monitored throughout therapy every 3 months or in parallel with imaging assessments, or at any time if clinically indicated.

Tumor response

Before starting chemotherapy the following imaging procedures should be performed:

- Conventional abdominal imaging - either multiphase contrast-enhanced CT, including arterial and portal venous acquisition phases, or MRI - should be performed within 4 weeks prior to initiation of chemotherapy.
- Thoracic imaging with a CT scan should be considered to be done at least once in every NEN, and should be definitively performed in patients in whom thoracic lesions have been identified by other imaging procedures (e.g. chest X-ray or somatostatin-receptor scintigraphy), in patients with rectal primaries and in patients with poorly differentiated or grade 3 NENs.

During chemotherapy the following imaging procedures are recommended:

- Abdominal imaging with the same technique as that performed at baseline, and thoracic CT scan if abnormal baseline findings, should be performed every 3 months while on chemotherapy or earlier if clinically indicated. Greater time intervals may be considered in individual patients with long-lasting disease stabilization. The use of RECIST 1.1 criteria to assess response and progression-free survival is recommended although not mandatory in patients not enrolled in clinical trials.

Drug interactions

Drug interactions should be carefully checked in cancer patients before initiating chemotherapy due to the narrow therapeutic index of most antineoplastic agents, and the potential for these interactions to lead to ineffective treatment or to severe or lethal side-effects. Here we summarize the most common known drug interactions of cytotoxic agents usually employed in the management of NENs. For more comprehensive information the reader is referred to the drugs SPCs.

Doxorubicin

Doxorubicin undergoes metabolism via CYP450 and is a substrate for the Pgp transporter. Concomitant administration of CYP450 inhibitors (e.g. ketoconazole, cimetidine, ritonavir, erythromycin, grapefruit juice, etc.) increase doxorubicin plasma concentrations and may thereby increase toxicity, whereas coadministration of CYP450 inducers (e.g. rifampicin, corticoids, phenytoin, carbamazepine, barbiturates or herbal preparations containing St John's Wort/Hypericum perforatum) reduce doxorubicin exposure and may decrease efficacy. Doxorubicin may reduce oral bioavailability/absorption of digoxin and antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate). Co-administration of heparin and doxorubicin can increase the rate of doxorubicin clearance. In addition, precipitates may form and lead to a loss of efficacy of both drugs [29,62].

Streptozocin

Streptozocin's metabolism and drug interactions have been barely studied in humans. Streptozocin has been reported to prolong the elimination half-life of doxorubicin [29].

Dacarbazine

Dacarbazine-solution is chemically incompatible with heparin, hydrocortisone, L-cysteine and sodium hydrogen carbonate. Dacarbazine is metabolised in the liver by CYP450 (CYP1A1, CYP1A2, and CYP2E1) to its active metabolites HMMTIC and MTIC. This has to be taken into account if other drugs are co-administered which are metabolised by the same hepatic enzymes (inducers of these enzymes could increase toxicity, and inhibitors could decrease efficacy) [29,62].

Temozolomide

TMZ does not undergo hepatic metabolism and exhibits low protein binding; it is therefore unlikely that it can affect the pharmacokinetics of other medicinal products. TMZ clearance is not altered by co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H₂ receptor antagonists, or phenobarbital. Co-administration with valproic acid was associated with a small decrease in TMZ clearance [29].

Capecitabine and 5-Fluorouracil

Various purines, pyrimidines, and antimetabolites (e.g. methotrexate, interferon, allopurinol, hydroxyurea, etc) have shown biochemical modulation of fluorouracil in *in vitro* test systems [29,38]. A synergistic cytotoxic interaction with folic acid modestly increases 5-FU efficacy, particularly in colon cancer, but it also leads to increased toxicity. Pretreatment with cimetidine prior to IV fluorouracil decreases 5-FU clearance and increases 5-FU plasma concentrations. Increased phenytoin plasma concentrations have been reported during concomitant use with fluoropyrimidines [62]. Concomitant use of allopurinol may decrease fluoropyrimidine efficacy. Marked elevations of prothrombin time and INR have been reported in some patients taking capecitabine or 5-FU concomitantly with warfarin. Caution should be taken when using capecitabine or fluorouracil in conjunction with medications that inhibit DPD activity including some common antiviral agents (sorivudine or brivudine). A 4-week waiting period is advised between end of treatment with these antivirals and start of fluoropyrimidine therapy [63].

Platinum compounds

Antioxidants such as sodium bisulphite might inactivate cisplatin before administration if present in IV fluids. Reduction of blood's lithium values has been reported in some cases following treatment with cisplatin, bleomycin and etoposide. Cisplatin and carboplatin may reduce the serum levels of phenytoin when used concurrently, likely due to reduced phenytoin absorption and/or increased metabolism. Phenytoin may also increase hepatic metabolism of platinum compounds, potentially decreasing their efficacy [29,62].

Etoposide

Etoposide Injection contains ethanol, benzyl alcohol and polysorbate, which may be toxic in infants and young children. Phenylbutazone and salicylates may displace etoposide from plasma protein binding and increase drug exposure. Cyclosporin and cisplatin may reduce etoposide clearance and thereby increase its toxicity. Concomitant phenytoin or phenobarbital therapy is associated with increased etoposide clearance and reduced efficacy. Concomitant warfarin therapy may result in increased INR values, so close monitoring is recommended in these patients [29,62].

Irinotecan

Concomitant administration of neuromuscular blocking agents should be done with caution. Irinotecan decreases phenytoin absorption. Concomitant administration of strong CYP450 3A4 (CYP3A4) inhibitors or inducers may increase toxicity or reduce efficacy. The use of these drugs should therefore be avoided if possible while on irinotecan therapy, or irinotecan doses shall be reduced or increased accordingly [29,62].

Pregnancy and lactation

Cytotoxic agents may be genotoxic and mutagenic, and can adversely affect human fertility or cause teratogenesis. Therefore, they should not be administered to pregnant women or those who are breast feeding. Men and women should use effective contraception during and up to 6 months after

treatment. Cryopreservation of sperm and/or ovarian tissue may be offered to fertile patients with potentially curative disease.

All other Antibes Consensus Conference participants

Arnold, R. (Munich, Germany); Bartsch, D.K. (Department of Surgery, Philipps University, Marburg, Germany); Baudin, E. (Département de Médecine, Gustave Roussy, 114, rue Édouard-Vaillant, Paris South University, Villejuif Cedex 94805, France); Borbath, I. (Service de Gastroenterologie, Cliniques Universitaires St-Luc, Bruxelles, Belgium); Capdevila, J. (Vall d'Hebron University Hospital, Teknon Institute of Oncology, Barcelona, Spain); Couvelard, A. (Service de Pathologie, Hôpital Bichat, Paris, France); Cwikla, J.B. (Department of Radiology, Faculty of Medical Sciences, University of Warmia and Mazury, Olsztyn, Poland); Davies, P. (Neuroendocrine Tumour Unit, Royal Free Hospital, London, United Kingdom); Delle Fave, G. (Department of Digestive and Liver Disease, Ospedale Sant' Andrea, Rome, Italy); Ferone, D. (Department of Endocrine and Metabolic Sciences, University of Genoa, Genoa, Italy); Grozinsky-Glasberg S. (Neuroendocrine Tumor Unit, Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel); Gorbunova, V. (Department of Oncology, Institution of Russian Academy of Medical Sciences); Gross, D. (Department of Endocrinology & Metabolism, Hadassah University Hospital, Mevasseret Tsion, Israel); Grossman, A. (Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, United Kingdom); Hicks R.J. (Cancer Imaging, the Peter MacCallum Cancer Centre, Melbourne); Hörsch, D. (Gastroenterology and Endocrinology Center for Neuroendocrine Tumors Bad Berka, Bad Berka, Germany); Tiensuu Janson, E. (Department of Endocrine Oncology, Uppsala University Hospital, Uppsala, Sweden); Jensen, R.T. (Digestive Diseases Branch, NIH, Bethesda, Md., USA); Kaltsas, G. (Department of Pathophysiology, Division of Endocrinology, National University of Athens, Athens, Greece); Knigge, U. (Neuroendocrine Tumor Center of Excellence, Rigshospital, Copenhagen University Hospital, Copenhagen, Denmark); Kos-Kudla, B. (Department of Endocrinology, Medical University of Silesia, Katowice, Poland); Krenning, E.P., (Cyclotron Rotterdam BV, Erasmus MC, Rotterdam, The Netherlands); Kwekkeboom, D.J. (Department of Internal Medicine, Division of Nuclear Medicine, ENETS Centre of Excellence Rotterdam, Erasmus MC, Rotterdam, The Netherlands); Niederle, B. (Department of Surgery, Medical University of Vienna, Vienna, Austria); Nieveen van Dijkum, E.J.M. (Department of Surgery, Academic Medical Center, Amsterdam, the Netherlands); Öberg, K. (Department of Medical Sciences, Endocrine Oncology Unit, University Hospital, Uppsala, Sweden); O'Toole (D. NET Centre, St. Vincent's University and Department of Clinical Medicine, St James Hospital and Trinity College, Dublin, Ireland); Pape, U.-F. (Department of Hepatology and Gastroenterology, Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany); Pascher, A. (Department of Surgery, Charité-Universitätsmedizin Berlin, Berlin, Germany); Perren A. (Institute of Pathology, University of Bern, Switzerland); Ramage, J. (Gastroenterology Department, Hampshire Hospitals NHS Trust, Hampshire, United Kingdom); Reed, N. (Beatson Oncology Centre, Gartnavel General Hospital, Glasgow, United Kingdom); Rindi, G. (Institute of Anatomic Pathology, Policlinico A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy); Ruszniewski, P. (Department of Gastroenterology, Beaujon Hospital, Clichy, France); Scoazec, J.-Y. (Services de pathologie morphologique et moléculaire, Département de biologie et pathologie médicales, Gustave Roussy Cancer Campus, Villejuif, France); Sundin, A. (Department of Radiology, Inst. Surgical Sciences, Uppsala University, Uppsala University Hospital, Uppsala, Sweden); Toumpanakis, C. (Neuroendocrine Tumour Unit, Royal Free Hospital, London, United Kingdom); Vullierme M.-P. (Service de Gastroentérologie, Hôpital Beaujon, Clichy, France); Welin, S. (Department of Medical Sciences, Endocrine Oncology, Uppsala University, Sweden); Wiedenmann, B. (Department of Hepatology and Gastroenterology, Campus Virchow Klinikum, Charité Universitätsmedizin Berlin, Berlin, Germany)

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Table 1. Streptozocin-based chemotherapy dosing regimens

Reference	Treatment regimen			
Moertel et al [5]	STZ	500 mg/m ²	days 1-5	q 6 weeks
	DOX	50 mg/m ²	days 1&22	
Eriksson et al [6]	STZ	500 mg/m ²	days 1-5,	q 3 weeks
		1 g/m ²	then day 1	
Moertel et al [5]	DOX	40 mg/m ²	day 3,	
			then day 1	
Moertel et al [5]	STZ	500 mg/m ²	days 1-5	q 6 weeks
	5-FU	400 mg/m ²	days 1-5	
Eriksson et al [4]	STZ	500 mg/m ²	days 1-5,	q 3 weeks
		1 g/m ²	then day 1	
	5-FU	400 mg/m ²	days 1-3,	
			then day 1	

STZ = Streptozocin; DOX = doxorubicin; 5-FU = 5-fluorouracil

Table 2. Platinum-based chemotherapy dosing regimens

Reference	Treatment regimen			
Mitry et al [23]	Cisplatin	45 mg/m ²	days 2-3	q 4 weeks
	Etoposide	100 mg/m ²	days 1-3	
Di Meglio et al [25]	Carboplatin	AUC 4-6	day 1	q 3 weeks
	Etoposide	100 mg/m ²	day 1-3	
Bajetta et al [16]	CAPOX			q 3 weeks
	- Oxaliplatin	130 mg/m ²	day 1 (iv)	
Hadoux et al [17]	- Capecitabine	1000 mg/m ² /12h	days 1-14 (po)	
	FOLFOX			q 2 weeks
Hentic et al [18]	- Oxaliplatin	85 mg/m ²	day 1	
	- Leucovorin	400 mg/m ²	day 1	
	- 5-FU iv bolus	400 mg/m ²	day 1	
	- 5-FU ci 46h	2400 mg/m ²	day 1	
Hentic et al [18]	FOLFIRI			q 2 weeks
	- Irinotecan	180 mg/m ²	day 1	
	- Leucovorin	400 mg/m ²	day 1	
	- 5-FU iv bolus	400 mg/m ²	day 1	
	- 5-FU ci 46h	2400 mg/m ²	day 1	

AUC – area under the curve; ci - continuous intravenous infusion; 5-FU – 5-fluorouracil; FOLFIRI – irinotecan, folinic acid and infusional 5-FU; FOLFOX – oxaliplatin, folinic acid and infusional 5-FU; iv – intravenous administration; po – oral administration; CAPOX – oxaliplatin and capecitabine.

Table 3. Dacarbazine and Temozolomide-based chemotherapy dosing regimens

Reference	Treatment regimen			
Olsen et al [7]	Temozolomide	200 mg/m ²	days 1-5	q 4 weeks
Ekeblad et al [8]				
Strosberg et al [10]	Temozolomide	175-200 mg/m ²	days 10-14	q 4 weeks
	Capecitabine	750 mg/m ² /12h	days 1-14	
Ramanathan et al [14]	Dacarbazine	850 mg/m ²	day 1	q 4 weeks
Mueller et al [15]	Dacarbazine	650 mg/m ²	day 1	q 4 weeks

Table 4. Toxicity of most commonly used chemotherapy regimens in NENs

Toxicity	STZ-DOX		STZ-5FU		CIS-VP16		CAPOX		FOLFOX		FOLFIRI		TEM		TEM-CAP		Dacarbazine	
	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4	all grades	grade 3-4
Nausea							62	5	64	5	72	13					31	0
Vomiting	80	20	81	41	76	40	43	5	43	4	50	10			43	0	44	7
Diarrhea	5	0	33	2			65	20	65	12	63	14					11	0
Mucositis	5	0	19	5			22	1	22	2	51	10					10	1
Skin toxicity							30	6	30	1	25	2			35	0		
Fatigue							38	6	21	4	46	4					5	0
Neurotoxicity					72	0	57	5	57	4	10	0						
Hear loss					14	0												
Renal toxicity			29	7	6	0									6	0		
Leucopenia	57		56	25	72	42							15	3			8	
Neutropenia					70	64	27	7	58	43	76	24	6	3	71	8		
Thrombocytopenia	0		8	6	24	12	23	7	24	4	16	0	37	14	74	11	3	
Anemia					33	12	54	3			42	3	32	3	63	3	5	

STZ = Streptozocin; CAP = Capecitabine; CAPOX = oxaliplatin and capecitabine; CIS-VP16 = cisplatin and etoposide; DOX = doxorubicin; 5-FU = 5-fluorouracil; FOLFIRI = irinotecan, folinic acid and infusional 5-FU; FOLFOX = oxaliplatin, folinic acid and infusional 5-FU; iv – intravenous administration; po – oral administration; TEM = Temozolomide; TEM-CAP = Temozolomide and Capecitabine.

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