CHEMOTHERAPY AND MOLECULAR TARGETED AGENTS TOXICITY/SAFETY

Rocio Garcia-Carbonero
Medical Oncology Department
Hospital Universitario 12 de Octubre
Universidad Complutense de Madrid
rgcarbonero@gmail.com
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OUTLINE

• Relevance of drug toxicity in cancer therapy

• Safety profile of commonly used cytotoxic and targeted agents in GEP-NENs

• Clinical management of most common side effects of systemic therapy
Relevance of Drug Toxicity in Cancer Therapy

- Burden of disease in NETs is high: patients already experience many tumor-related symptoms
- One of the aims of therapy is to improve symptom control
- QoL is often compromised by treatment-related toxicity

Important to differentiate drug toxicity from underlying symptoms

Effective AE management is essential to minimize risks, ensure treatment compliance and maximize treatment effect

Key Points for optimal Management of Toxicity

- Adequate baseline assessment and patient selection
- Proper monitoring, pre-emptive and supportive measures
- Optimization of dose and schedule

KNOW WHAT TO EXPECT
SAFETY PROFILE OF COMMONLY USED CYTOTOXIC AND TARGETED AGENTS IN GEP-NENS
Treatment compliance of targeted agents in Pivotal Studies in PanNETs

<table>
<thead>
<tr>
<th>Pivotal Studies in PanNET</th>
<th>EVEROLIMUS</th>
<th>SUNITINIB</th>
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<tbody>
<tr>
<td>Dose intensity</td>
<td>86%</td>
<td>91%</td>
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<tr>
<td>AEs leading to:</td>
<td></td>
<td></td>
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<tr>
<td>- Dose reduction</td>
<td>59%</td>
<td>31%</td>
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<tr>
<td>- Dose interruption</td>
<td>(DR + DI)</td>
<td>30%</td>
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<tr>
<td>- Treatment discontinuation</td>
<td>17%</td>
<td>17%</td>
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EVEROLIMUS Safety Profile

- **Mucositis**: most common AE reported in >60% of patients (G3-4: 7-9%). It usually occurs within the first 8 weeks of treatment, and resolves within 10-14 days of tx discontinuation.
- **Skin rash**: reported in 29–49% of patients, mostly mild to moderate in severity.
- **Diarrhea**: occurs in 30% of patients (G3-4: 3-7%).
- **Myelotoxicity**: anemia or thrombocytopenia occurs in < 20% of patients (G3-4: 5%)
- **Infections**: occur in ~20% of patients (G3-4: 2-7%, occasionally fatal). There is a risk of reactivation of latent hepatitis B virus infection.
- **Non-infectious pneumonitis**: occurs in 12-17% of patients (G3-4: 1-2%). Clinical symptoms such as dyspnea or cough are typical, but may be absent.
- **Metabolic abnormalities**: hyperglycemia (12-13%; G3-4: 5%), hyperlipidemia (39-66%) and hypophosphataemia (may cause muscle weakness)(40%; G3-4: 10%).
- **Renal function**: mild reversible creatinine elevation reported in ~ 20% of patients (G3-4: 1%)
- **Asthenia or fatigue**: reported in ~30% (G3-4: only 1-2%).
- **Peripheral oedema** occur in 13-20% of patients (G3-4 ≤1%).
SUNITINIB Safety Profile

- **Hypertension:** 26% of patients (G3-4: 10%); on-target AE associated with VEGF/VEGFR inhibition (class effect).
- **Neutropenia:** 29% of patients (G3-4: 12%). It is usually short-lived, uncomplicated (FN very uncommon).
- **Diarrhea:** occurs in 59% of patients (G3-4: 5%).
- **Nausea** (45%) and **vomiting** (34%) are generally mild or moderate in severity.
- **Fatigue** occur in ~30% of patients (G3-4: 5%). Usually develops during the first month of tx.
- **Dermatologic AEs:** hair and skin depigmentation (29%), hand-foot syndrome (23%; G3-4 6%), rash (18%).
- **Mucositis:** 48% (G3-4: 6%). It often occurs during the first month of tx.
- **Hypothyroidism:** 7% of patients, all G1-2. Greater incidence with prolonged exposure.
- **QTc prolongation:** observed in <0.1% of sunitinib-exposed patients (dose-dependent). Sunitinib should be used with caution in pts with a history of QT-interval prolongation, pre-existing cardiac arrhythmias or electrolyte disturbances. Pts with QTc >450 msec (males) or >470 msec (females) were excluded from the pivotal study.
- **Thromboembolic events** were not reported sunitinib-treated patients in the phase 3 pNET trial.
Distinct toxicities from specific cytotoxic drugs

- **Streptozocin**: renal toxicity
- **Doxorubicin**: cardiotoxicity, alopecia, emesis
- **Fluoropyrimidines (5FU, Cape)**: HFS, mucositis, GI toxicity
- **Cisplatin**: neurotoxicity, renal toxicity, ototoxicity, emesis
- **Oxaliplatin**: neurotoxicity (worsened with cold)
- **Carboplatin**: myelotoxicity, liver toxicity
- **Etoposide**: myelotoxicity, emesis, alopecia
- **Irinotecan**: diarrhea, cholinergic syndrome, alopecia
- **Temozolomide**: lymphopenia, liver toxicity

All cytotoxic drugs are associated to some degree of bone marrow and GI toxicities.
PREVENTION AND TREATMENT OF DRUG TOXICITY
BASELINE ASSESSMENT

Patient status

General
- Performance status
- Bone marrow reserve
- Liver and kidney function
- Nutritional status
- Comorbidities
- Concomitant medications
- Pregnancy and lactation
- Baseline symptoms
  - Fatigue
  - Weight (loss)
  - Diarrhoea
  - Oral hygiene & dental care

Treatment-specific requirements

Targeted therapies:
- **Sunitinib**
  - Blood pressure
  - Thyroid function tests
  - Urinalysis
  - EKG (QTc)
- **Everolimus**
  - Glucose / HbA1c
  - Viral hepatitis status
  - Respiratory parameters

Chemotherapy:
- **Platinum agents**
  - Peripheral neuropathy
- **Anthracyclines**
  - Cardiac function (MUGA)
Managing Diarrhea

Differential Diagnosis (other causes need to be considered and treated, often multifactorial)

- SSA-induced pancreatic exocrine insufficiency (PEI)
- Hormonal syndrome (carcinoid, VIP, gastrin,..)
- Pancreatic or bowel surgery
- Infection

Preventative measures

- Avoid caffeine, high lactose-containing, fatty or high-fibre foods
- Maintain adequate hydration

Treatment

- Oral or intravenous (re)hydration as indicated with fluids that contain water, salt, and sugar
- Oral anti-diarrheals (intensive loperamide therapy; SSA or opium derivatives in severe cases)
- Grade 3/4: interrupt until recovery to ≤Grade 1/2
  - Grade 3: reinitiate at same or lower dose, particularly if recurrent
  - Grade 4: reinitiate at lower dose or discontinue
# Managing Fatigue/Asthenia

## Differential Diagnosis (other causes need to be considered and treated, often multifactorial)
- Hypothyroidism
- Anemia
- Malignancy itself
- Depression
- Electrolyte imbalance and dehydration

## Preventative measures
- Ensure a consistent sleep cycle
  - Maintain activity levels during the day
  - Avoid excessive caffeine and alcohol
  - Adequate fluid and nutritional intake

## Treatment
- Grade 3-4: interrupt until recovery to ≤Grade 1-2
- Dose reductions may be considered, although they do not always have a major impact
- Consider intermittent dosing 2 weeks on / 1 week off for oral therapy
- Optimize treatment of anemia, hypothyroidism, etc..
Managing Hypertension

Differential Diagnosis
• Review past medical history (toxic habits, cardiovascular risk factors and comorbidities)
• Baseline clinical cardiovascular assessment: blood pressure (to differentiate whether or not drug-induced), organ assessment as needed if baseline hypertension

Preventative measures
• Actively screen for hypertension during treatment (may include home monitoring)
• General health measures if possible: avoid overweight and stress, encourage physical activity, control other cardiovascular risk factors (smoke, diabetes, hyperlipemia, …)

Treatment
• Treat as appropriate per standard guidelines
  – Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers
  – Dihydropyridine calcium channel blockers
• Grade 3/4: interrupt until recovery to ≤Grade 1/2
  – Grade 3: reinitiate at same or lower dose, particularly if recurrent
  – Grade 4: reinitiate at lower dose or discontinue
Managing Nausea and Vomiting

Differential Diagnosis
• Exclude other causes: disease (bowel obstruction, carcinomatosis, brain mets), drugs (opioids..), electrolyte disorders (hypercalcemia..), vestibular disfunction, ...

Preventative measures
• Antiemetic prophylaxis as per ASCO, NCCN or MASCC-ESMO guidelines
  - highly emetogenic (e.g., cisplatin, dacarbazine, STZ): neurokinin-1 antagonist (aprepitant, fosaprepitant, netupitant) + 5-HT-3 antagonist (granisetron, ondansetron, palonosetron, ..) and dexamethasone.
  - moderate emetogenic (e.g., oxaliplatin, carboplatin, doxorubicin, irinotecan, TMZ), 5-HT-3 antagonists and dexamethasone.
  - low emetogenic (e.g., 5-FU), corticosteroids alone.
• Caution with CYP3A4 interaction (e.g., ondansetron)

Treatment
• Early treatment (metoclopramide, olanzapine, corticoids,..) and supportive measures to avoid dehydration and electrolyte disorders. Monitor weight and ensure adequate nutrition.
• Grade 3/4: interrupt until recovery to ≤Grade1. Intensification of antiemetic prophylaxis shall be implemented in subsequent cycles. No dose adjustments are generally required.
Toxicity of Cytotoxic and Targeted Agents
TAKE HOME MESSAGES

• Pay close attention to drug-induced toxicity as it has a major impact on patient’s treatment adherence and QoL

• Adequate toxicity management is key for patients to remain on therapy for as long as they continue to derive benefit

• Assessment of emergent toxicities requires a good baseline assessment of relevant medical history, concurrent medication and disease-related symptoms

• Follow available guidelines and clinical judgement for proper management of toxicities with supportive measures, dose delays and/or reductions, or schedule adjustments as needed

• Patients must be properly informed regarding expected toxicities and how to handle them. A fluent communication between patient and medical team is essential for optimal management.