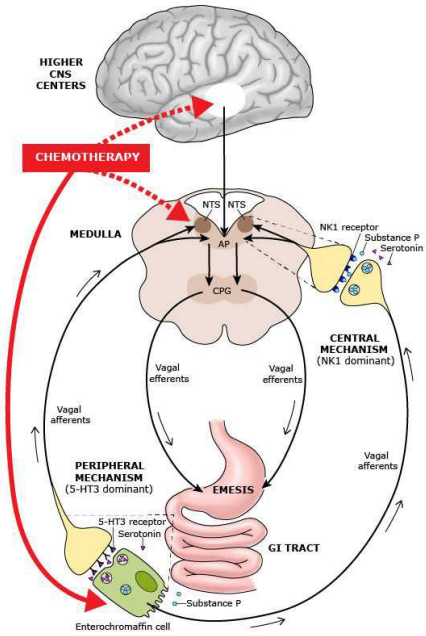
Chemotherapy induced nausea and vomiting (CINV)

General Overview



- 3 types of CINV
  - Acute emesis: <1 – 2hours after chemo and peaks in 4-6 hours
  - Delayed emesis: >24h after chemo (less severe but lasts longer)
  - Anticipatory emesis: prior to treatment (conditioning)

- Pathofysiology: most important neutrotransmitters involved: dopamine, serotonine and substance P (binds NK1-R)
- Delayed emesis mostly after cisplatin, carboplatin, cyclophosphamide, anthracyclines, oxalplatin
- Vomiting after chemo: also think of obstruction, brainM+, metabolic disturbances, concomitant medication
- Predictive factors:
  - Patient-related factors:
    - Emesis with prior chemotherapy
    - Women
    - Younger patients
    - In case of history of alcohol abuse: less CINV
    - Rapid metabolizers of 5-HT3 antagonists and certain polymorphisms in 5HT3 R
    - Patients with acute emesis are more likely to have delayed emesis
    - History of motion sickness may predispose to anticipatory emesis

  - Chemotherapy agent:

RISK LEVEL	IV AGENT
High (>90%)	Anthracyclines/cyclophosphamide combination Cisplatin, dacarbazine, cyclophosphamide ≥1500 mg/m²
Moderate (30-90%)	Carboplatin, cyclophosphamide <1500 mg/m², doxorubicin, epirubicin, trastuzumab-deruxtecan, ifosfamide, irinotecan, liposomal irinotecan, oxaliplatin, temozolomide, trabectidin
Low (10-30%)	Aflibercept, cabazitaxel, cetuximab, docetaxel, enfortumab vedotin, eribulin, etoposide, 5-FU, gemcitabine, methotrexate, mitomycin, mitoxantrone, nab-paclitaxel, paclitaxel, panitumumab, pegylated liposomal doxorubicin, pemetrexed, pertuzumab, temsirolimus, topotecan, trastuzumab-emtansine,
Minimal (>10%)	Atezolizumab, avelumab, bevacizumab, bleomycin, cemiplimab, durvalumab, ipilimumab, nivolumab, pembrolizumab, ramucirumab, trastuzumab, vinblastine, vincristine, vinorelbine

RISK LEVEL	ORAL AGENT
Moderate or high (>30%)	Abemaciclib, avapritinib, cabozantinib, crizotinib, cyclophosphamide, imatinib, Lenvatinib, lomustine, niraparib, procarbazine, ribociclib, rucaparib, TAS-102, temozolomide, vinorelbine
Minimal or Low (<30%)	Afatinib, alectinib, alpelisib, axitinib, capecitabine, cobimetinib, dabrafenib, dasatinib, encorafenib, entrectinib, erdafitinib, erlotinib, etoposide, everolimus, gefitinib, ibrutinib, ivosidenib, lapatinib, Larotrectinib, lorlatinib, melphalan, methotrexate, neratinib, nilotinib, Olaparib, Osimertinib, palbociclib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, talazoparib, tazemetostat, topotecan, trametinib, vandetanib, vemurafenib, venetoclax

- For combination regimens, the emetogenic level is determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents (example: cyclo and doxo both moderately but in combination highly emetogenic)

Classification anti-emetics

- *High therapeutic index*:
  - **5HT3 antagonist**:
    - ondansetron (Zofran®), granisetron (Kytril ®), palonosetron (Aloxi®), tropisetron (Novaban®)
    - Side effects: QT prolongation, constipation (!), headache, ↑ transaminases
  - **Neurokinin-1 receptor antagonist**
    - Aprepitant (Emend® PO) 125-80-80 PO, Fosaprepitant (Ivemend®) 150 mg IV
    - Netupitant (Akynzeo® = netupitant + palonosetron) PO
  - **Steroids**
- *Low therapeutic index*: metoclopramide (Primperan®), alizapride (Litican®), domperidone (Motilium®), itopride (Itoprom), haloperidol (Haldol®), lorazepam (Temesta®), olanzapine (Zyprexa®)
- First generation 5-HT3 antagonists have equal activity. For moderately emetogenic chemotherapy the second generation 5-HT3 antagonist palonosetron (long half life: 40h) is recommended according to the NCCN guidelines (MASCC, ESMO and ASCO do not specify a preferred 5-HT3 antagonist). For highly emetogenic unclear if palonosetron is superior (not reimbursed in Belgium in combination with aprepitant).

- Reimbursement (Belgium):
  - Palonosetron: Moderate / high emetogenic (>30%), not in combination with aprepitant
  - First generation 5HT3: Moderate and high emetogenic schedules (>30%)
  - Aprepitant:
    - Cyclophosphamide IV >1500 mg/m², dacarbazine, cisplatin > 20mg/m² (combination with 5-HT3 d1 and steroid D1-4)
    - Association cyclophosphamide ≥ 500 mg/m² with anthracycline
    - Increased risk and carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan or methotrexate
  - Netupitant + palonosetron (Akynzeo): same as aprepitant but no combination with other 5HT3 or apretitant allowed

Guidelines UZA

Emetic risk	Day 1	Day 2	Day 3	Day 4
High*	Aprepitant 125 PO Zofran® 8 mg IV Dexamethasone 10 mg IV Olanzapine 5 mg PO	Aprepitant 80 Dexa 8mg Olanzapine	Aprepitant 80 Dexa 8mg Olanzapine	Dexa 8mg Olanzapine
	Fosaprepitant 150 IV Dexamethasone 10 mg IV Olanzapine 5 mg PO	Dexa 8mg Olanzapine	Dexa 8mg Olanzapine	Dexa 8mg Olanzapine
	Akynzeo® Dexamethasone 10 mg IV Olanzapine 5 mg PO	Dexa 8mg Olanzapine	Dexa 8mg Olanzapine	Dexa 8mg Olanzapine
Moderate (non carbo)	5HT3 antagonist Dexamethasone 10 mg IV	Dexa 8 mg	Dexa 8 mg	
Moderate (carbo AUC ≥ 4)	NK1-R antagonist 5HT3 antagonist Dexamethasone 10 mg IV			
Low	Dexa 8 mg			

*for anthracyclines/cyclophosphamide or carboplatin combinations only steroids on day 1

- For multiday chemotherapy patients should receive the agent of the highest therapeutic index daily during chemo and for 2 days thereafter.
- Adjunctive drugs: lorazepam can be useful but is not recommended as single agent
- Cannabinoids: insufficient evidence
- Radiotherapy:

Emetic risk	Day 1
High (total-body)	5HT3 antagonist and dexa before each fraction and on the day after each fraction (if no RT planned on that day)
Moderate: upper abdomen, craniospinal	5HT3 antagonist before each fraction (with or without dexa), before the 5 first fractions
Low: brain, H&N, thorax, pelvis	Brain: breakthrough dexa therapy H&N, thorax, pelvix: breakthrough with 5HT3, dexa
Minimal: extremities, breast	breakthrough with 5HT3, dexa

References

1) ASCO guideline:
2) ESMO guideline
3) MASCC guideline

Update: December 2023