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Supportive Care Makes Excellent Cancer Care Possible #MASCC18

NAUSEA AND VOMITING AFSOS GUIDANCE

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Disclosures

- Consultant / Advisory Boards / Speaker: Tesaro, Helsinn, Sanofi, Roche, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, AMGEN, Pierre Fabre Oncologie, Vifor Pharma
- Associations: ESMO, ASCO, MASCC, AFSOS, AESCO

Table of Contents

Introduction / context

- Chemotherapy Induced Nausea and Vomiting (CINV) are one of the side effects feared by patients who initiate cancer chemotherapy treatment.
- There is a gap between patients' and caregivers' perceptions that can be detrimental in optimizing antiemetic treatments.
- Poor control of NVCI has a major impact on quality of life, daily activities, professional activities, social and relational life.
- NVCI can cause serious metabolic complications: acute functional renal failure, chronic renal failure after sequella, ionic disorders, weight loss, denutrition.

Introduction : Warning

The members of the "Nausea and Vomiting Chemo-Induced (NVCI): Management" working group have chosen **not to modify** the emetogenic level of certain chemotherapy molecules or protocols as proposed in the updated international recommendations (ESMO-MASCC, ASCO, NCCN).

In particular, the group members chose to keep anthracycline-cyclophosphamide, carboplatin (AUC 4), epirubicin (> 90 mg/m2) and doxorubicin (> 60 mg/m2) as moderately emetogenic.

The reasons for this choice are **primarily educational**: so that there is no exception to the rule "The most emetogenic molecule gives the overall level of chemotherapy protocol".

On the other hand, the main motivation of the international recommendations for the modification of the emesis level of molecules seems to be to allow the introduction of an anti-NK1 in the prophylaxis of these same molecules. However, since 2013, **AFSOS standards propose an anti-NK1 for all moderately emetogenic protocols**.

Finally, by keeping these molecules as moderately emetogenic, there is **no need to prescribe corticosteroids** for primary prophylaxis (thus allowing cortisonic savings).

The members of the "Nausea and Vomiting Chemo-Induced (NVCI): Management" working group

CINV Clinical Presentation

Name	Features
Anticipated	Before Chemotherapy Administration
Acute	During the 24 hours after Chemotherapy Administration
Delayed	After 24 hours Following Chemotherapy Administration
Refractory	CINV Despite Right Treatment

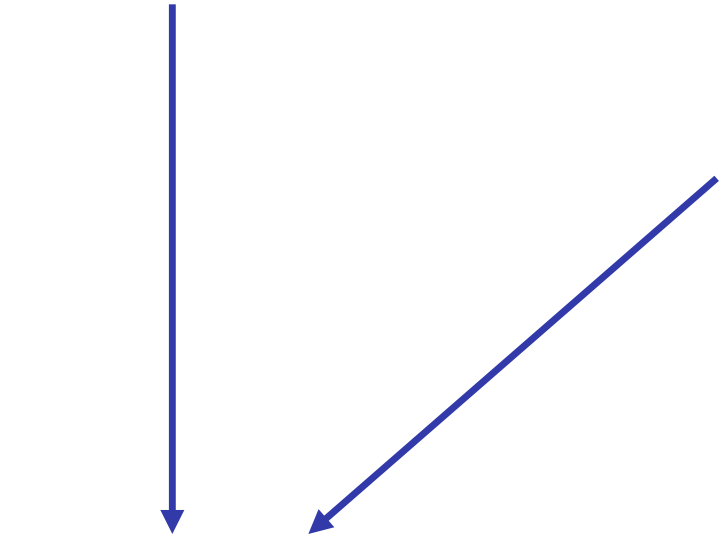
CINV Classification

	Nausea	Vomiting
Grade 1	Appetite Loss	1 Episode of Vomiting / 24h
Grade 2	Decrease in food intake No weight loss Without dehydration Without undernutrition	2 - 5 Episodes of Vomiting / 24h
Grade 3	Insufficient intakes (caloric and/or hydric) Nutrition by tube, parenteral and/ or hospitalization required	≥ 6 Episodes of Vomiting / 24h
Grade 4	-	Life-threatening risk
Grade 5	-	Death

D'après le NCI-CTAE v 4.03
(National Cancer Institute-Common Terminology Criteria for Adverse Events)

CINV Risk Factors

Emetogenic risk chemotherapy



CINV

Individual Risk Factors

- Age < 55-60 years
- Female sex
- Background :
- Morning Nausea
- Pregnant Nausea
- Motion sickness
- Early Nausea
- Sleep < 7 hours the day before chemo
- Anxious subject
- Subject who thinks he is at high risk for NVCI
- History of NVCI in previous chemotherapy cycles

Individual protective factors

- Alcohol Intake

Management

Name	Features
Primary Prophylaxy	Preventive treatment put in place from the 1st cycle of chemotherapy
Secondary Prophylaxy	Preventive treatment put in place following the occurrence of NVCI during the previous chemotherapy cycle
Rescue Treatment	Treatment for NVCI despite well-managed prophylaxis

Drugs (cf. annexe)

- Setrons (Anti-5-HT3)
  - Antagonists of Serotonine Type 3 Receptor
- NK-1 Inhibitors
  - Antagonists of Neurokinin type 1 Receptors
- Steroïds
- Anti-D2
  - Antagonists of Dopamin type 2 Receptors
- Psychotrops
  - Benzodiazepins
  - Neuroleptics

Advice for Patients

Hygieno-Dietetics Rules

- Promote hydration: prevention of kidney failure
- Splitting the diet: 6 to 8 small meals and/or snacks per day
- Offer small cold meals to avoid strong odours
- Avoid foods that are too fatty, fried or spicy
- Choose foods that are easy to digest
- Offer to eat slowly
- Offer drinks to patients' taste between meals: water, infusions, apple juice, Coca Cola® (degassed or not)…
- If necessary, use a straw in a closed cup to facilitate small sips and avoid odours.
- Maintain a sitting position for 30 minutes after eating; if lying down, prefer the right side to promote gastric emptying

Non-Drugs Solutions

Acupuncture

- In addition to well-managed drug prophylaxis (grade B recommendation)
  - Electrostimulation > simple acupuncture: reduces the incidence of acute vomiting
  - Acupressure reduces the severity of acute nausea
  - No data on delayed events
  - Points Used: 6MC +++ +/- 36E and 4Rp
  - Acupuncture session: the day before or qq hours after chemotherapy
  - Adverse reactions: all related to electrostimulation: transient rash, skin irritation at electrode points, electric shock, aggravation of paresthesia in patients with peripheral neuropathy.

Other Therapeutics

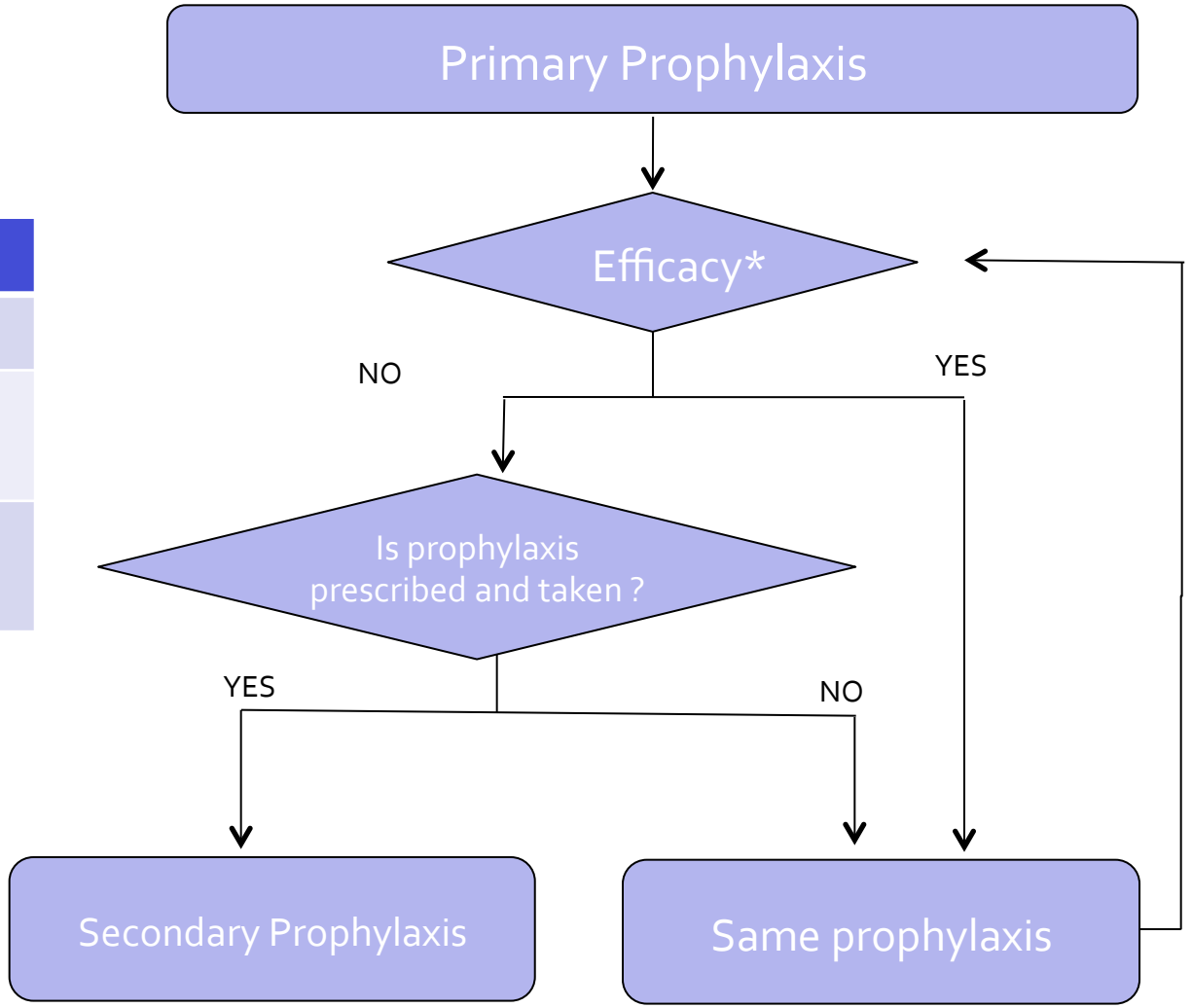
Low Level of Evidence :

- Ginger
- Desmodium
- Mint Alcohol
- Homeopathy
- …

Warning with Drug-Drug Interactions

Implementation of management

At any time
Patient counseling
Rescue Treatments
+/- acupuncture



* = efficacy = Nausea ≤ grade 1 or < 2,6 mm on Analogic Numeric Scale and Vomiting grade 0

Define Primary Prophylaxis

1. Define the Emetogenic Level of Drugs

2. Define the Emetogenic Level of Protocol

3. Prophylaxis in Function the Emetogenic Level of Protocol

4. Adaptation according to the patient risk factors

1. Emetogenic Level of Drugs

IV Drugs

High Emetogenic (90 %)
Carmustine
Cisplatine
Cyclophosphamide (> 1,5 g/m²)
Dacarbazine
Mechlorethamine
Streptozocine

1. Emetogenic Level of Drugs

IV Drugs

Moderate Emetogenic (30 to 90%)	
Alentuzumab	Epirubicine
Azacitidine	Idarubicine
Bendamustine	Ifosfamide
Carboplatine	Irinotecan
Clofarabine	Oxaliplatine
Cyclophosphamide (<1,5 g/m²)	Romidepsine
Cytarabine (> 1 g/m²)	Temozolomide*
Daunorubicine	Thiotepa
Doxorubicine	Trabectidine

* Pas de données en IV / extrapolation avec le per os

1. Emetogenic Level of Drugs

IV Drugs

Low Emetogenic (10 to 30%)	
Aflibercept	Gemcitabine
Atezolizumab	Ipilimumab
Belinostat	Ixabepilone
Blinatumomab	Methotrexate
Bortezomib	Mitomycine
Brentuximab	Mitoxantrone
Cabazitaxel	Nab-paclitaxel
Carfilzomib	Paclitaxel
Catumaxumab	Panitumumab
Cetuximab	Pemetrexed
Cytarabine < 1 g/m2	Pertuzumab
Doxorubicine Liposomale Pegylatée	Temsirolimus
Docetaxel	Topotecan
Eribuline	Trastuzumab-emtansine
Etoposide	Vinflunine
5-Fluorouracile	

1. Emetogenic Level of Drugs

IV Drugs

Very Low Emetogenic (< 10%)	
Bevacizumab	Pembrolizumab
Bleomycine	Pixantrone
Busulfan	Pralatrexate
2-Chlorodeoxyadenosine	Ramucirumab
Cladribine	Rituximab
Daratumumab	Trastuzumab
Fludarabine	Vinblastine
Nivolumab	Vincristine
Obinutuzumab	Vinorelbine
Ofatumumab	

1. Emetogenic Level of Drugs
Oral Drugs

High Emetogenic (90 %)	
Hexamethylmelamine	Procarbazine

Moderate Emetogenic (30 à 90%)	
Bosutinib	Imatimib
Cabozantinib	Lenvatinib
Ceritinib	TAS-102
Crizotinib	Temozolomide
Cyclophosphamide	Vinorelbine

1. Emetogenic Level of Drugs

Oral Drugs

Low Emetogenic (10 à 30 %)		
Afatinib	Idelalisib	Regorafenib
Alectinib	Ixazomib	Sonidegib
Axatinib	Lapatinib	Sunitinib
Capecitabine	Lenalidomide	Tegafur Uracil
Cobimetinib	Olaparib	Thalidomide
Dabrafenib	Osimertinib	Trametinib
Dasatinib	Nilotinib	Vandetanib
Everolimus	Palbociclib	Vorinostat
Etoposide	Panobinostat	Venetoclax
Fludarabine	Pazopanib	
Ibrutinib	Ponatinib	

1. Emetogenic Level of Drugs
Oral Drugs

Very Low Emetogenic (< 10%)	
Chlorambucile	Pomalidomide
Erlotinib	Ruxolitinib
Gefitinib	Sorafenib
Hydroxyurée	6-Thioguanine
Melphalan	Vemurafenib
Methotrexate	Vismodegib
Moutarde à la L-Phenylalanine	

2. Define the protocol Emetogenic level

- Most emetogenic molecule gives the overall level of the chemotherapy protocol
- Emetogenic levels are not added
  - If protocol with 2 moderately emetogenic drugs then the protocol is moderately emetogenic.

3. Primary Prophylaxis of Acute and Delayed CINV
Several options (in no order of preference)

High Emetogenic Chemo(HEC)

Day 1	Days 2,3,4
✓ Aprepitant 125 mg ✓ Setron (au choix annexe 1) ✓ Steroïds	✓ Aprepitant 80 mg (D2-D3) ✓ Steroïds
or	
✓ Rolapitant 180 mg ✓ Setron (Optional Annex 1) ✓ Steroïds	✓ Steroïds
or	
✓ Nepa* (Netupitant 300 palonosetron 0,5) ✓ Steroïds	✓ Steroïds

* : NEPA : in France for Cisplatin based regimen

3. Primary Prophylaxis of Acute and Delayed CINV
Several options (in no order of preference)

Moderate Emetogenic Chemo (MEC)

Jour 1	Jours 2,3
✓ Aprepitant 125 mg ✓ Setron (Optional Annex 1) ✓ Steroïds	✓ Aprepitant 80 mg (J2-J3)
or	
✓ Rolapitant 180 mg ✓ Setron (Optional Annex 1) ✓ Steroïds	

3. Primary Prophylaxis of Acute and Delayed CINV
Several options (in no order of preference)

Low Emetogenic Chemo (LEC)

Jour 1
✓ Anti-D2
or
✓ Steroïds
or
✓ Setron (Optional Annex 1)

Very Low Emetogenic Chemo (VLEC)

No Routine Primary Prophylaxis

4. Adaptation of prophylaxis serving patient risk factors

CINV Individual Risk Factors

Individual Risk Factors

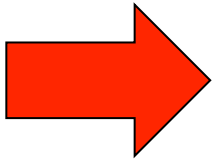
- Age < 55-60 years
- Female sex
- Background :
- Morning Nausea
- Pregnant Nausea
- Motion sickness
- Early Nausea
- Sleep < 7 hours the day before chemo
- Anxious subject
- Subject who thinks he is at high risk for NVCI
- History of NVCI in previous chemotherapy cycles

Individual protective factors

- Alcohol Consumption

4. Adaptation of prophylaxis

In Case of Many Risk Factors



« Upgraded » Prophylaxis :

- Application of primary prophylaxis at the upper emetogenic level …
- From the first cycle

« Upgraded » Primary Prophylaxis

- HEC : HEC prophylaxis HEC + Olanzapine
- MEC : HEC prophylaxis
- LEC : MEC prophylaxis
- VLEC : LEC prophylaxis

HEC : High Emetogenic Chemo
MEC : Moderate Emetogenic Chemo
LEC : Low Emetogenic Chemo
VLEC : Very Low Emetogenic Chemo

Secondary Prophylaxis

= Add a Drug

(without order of preference / not previously prescribed)

- Anti-NK1
- Setron
- Steroïds
- Anti –D2
- Psychotropes :
  - Neuroleptics : Olanzapine / Haloperidol (Off Label Use)
  - benzodiazepines
- Cannabinoides (not available in France)

Rescue Treatments

During Chemo

- **Setron :** dose optimization (up to 16 mg single dose)
- **Anti D2**
  - Alizapride : 5 mg/Kg/jour 15 minutes IV
  - Or Metoclopramide : 30 mg 15 mn IV (max dose 0,5/Kg/j)
- **Steroïds :** NO
- **Benzodiazepine :** if failure (per os or intravenous)

During the 24 first hours

- **Setron +/- Anti-D2 +/- Benzodiazepine**

In the Delayed Phase

- **Anti-D2 +/- Benzodiazepine**

Special cases

Continuous Chemotherapy

- Example : capecitabine
  - No long course steroids
  - Anti-D2 one hour before chemotherapy
  - If failure: daily setron

Special Cases

- Trabectidine
  - Primary Prophylaxis : setron (at choice) + Steroïds
- Ifosfamide
  - Primary Prophylaxis : setron (at choice) + Steroïds

- **Aprepitant:** to avoid absolutely with these 2 molecules because of the interaction and the increased risk of toxicity.

- **Rolapitant:** no published clinical data (ongoing studies). Pharmacological and preclinical data (1,2) support a lack of interaction with these 2 molecules. Its use cannot be recommended as it stands but must be examined according to the intensity of the NVCI and the interest of the patient, in particular the prognosis.

(1) Varuby®. European Medicines Agency. Summary of Product Characteristics. Accessed October 6, 2017.
(2) Wang et al. Poster 11-07-P MASCC 2015.

Multi-Day Chemo (BEP or TPF)

- If aprepitant
  - 125 mg D1 then 80mg next days

  (continue 2 days after the last injection of HEC* ou de MEC**)

- No Data with NEPA, palonosetron ou rolapitant

* HEC : High Emetogenic Chemo
** MEC : Moderate Emetogenic Chemo

Task Force

Coordination 2017 Update

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Annex

Drugs Solutions

Sétrons (1/2)

Molécules, voies d'administration et posologies disponibles (IV = Per os)

- **Granisetron**
  - Comprimé pelliculé : 1mg, 2 mg (générique, KYTRIL®)
  - Solution injectable : 3 mg/3ml (générique, KYTRIL®)
- **Ondansetron**
  - Comprimé pelliculé : 4 mg, 8 mg (générique, ZOPHREN®)
  - Comprimé lyoc ou orodispersible : 4 mg, 8 mg (générique, ZOPHREN®)
  - Sirop : 4 mg/5 ml (ZOPHREN®)
  - Suppositoire : 16 mg (ZOPHREN®)
  - Film orodispersible : 4 mg, 8 mg (SETOFILM®)
  - Solution injectable : 2 mg/ml (générique, ZOPHREN®)
- **Palonosetron**
  - Solution injectable : 250 µg (ALOXI®)

Sétrons (2/2)

- Antagonistes des récepteurs à la sérotonine de type 3

- Effets indésirables fréquents :
  - Constipation, céphalées (grades faibles)
  - ↗ transitoire et asymptomatique des ASAT et ALAT

- Risque de torsade de pointe (↗ QT)
  - ECG indispensable avant première cure de chimio

Anti-NK 1

- Antagonistes des récepteurs aux neurokinines de type 1

- Molécules disponibles :
  - **Aprépitant :** J1 : 125 mg + J2 et J3 : 80 mg
  - **Nétupitant** (disponible uniquement en association avec palonosétron : NEPA) : J1 : 300 mg/0,5mg
  - **Rolapitant :** J1 : 180 mg

Remarque : Netupitant et Rolapitant possèdent une longue demie vie. Leur prise unique à J1 permet une prophylaxie des NVCI retardés sur plusieurs jours.

Corticoïdes

- Molécule de référence : dexaméthasone (DXM)
- Pas de différences entre corticoïdes à posologies équivalentes (cf. infra)
- Prise unique / p*er os* = IV
- Les corticoïdes utilisés dans le traitement des hémopathies malignes lymphoïdes pourront être administrés aux horaires des antiémétiques afin d'éviter une dose de corticoïdes trop importante.

Corticoïdes	Posologie (mg)	Posologies (mg)
Dexaméthasone	12	8
Méthylprednisolone	64	44
Prednisone / Prednisolone	80	55
Hydrocortisone	320	220

Anti D2

- Antagoniste de la dopamine
- Molécules disponibles :
  - Métoclopramide (per os, suppositoire, injectable)
  - Métopimazine (per os, suppositoire, injectable)
  - Alizapride (per os et injectable)

NB : Dompéridone à éviter car pas de données dans la littérature et risque de troubles du rythme cardiaque

Psychotropes

- Benzodiazépines (BZD)
  - Préférer les BZD à demi-vie courte (ex : alprazolam)
- Neuroleptiques
  - Olanzapine : 1 cp de 5 mg par jour pendant 5 jours

Contributeurs

Coordination Mise à jour 2017

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