

la fréquence des NVCI chez des patients recevant des chimiothérapies hautement émétisantes tant en phase aiguë (74% vs. 45%, $P=0.002$) que retardée ($<3j$: 42% vs. 25%, $P=0.002$) (24). La posologie de 5 mg/jour a une efficacité similaire à celle utilisée initialement (10 mg par jour) avec moins de somnolence (18,19). Le surcoût est par ailleurs modeste. Les résultats de l'étude J-Force présentée en 2019 à l'ASCO (essai de phase III randomisé, contre *placebo*, évaluant l'efficacité de l'olanzapine à 5 mg ajouté au triplet sétron, corticoïde et inhibiteur de NK-1) chez des patients recevant du cisplatine à plus de 50 mg/m² ont montré une amélioration de plus de 13% du contrôle complet en phase aiguë et retardée avec une excellente tolérance^F. Une revue systématique et méta-analyse publiée en 2019 (ESMO Open) regroupant 11 études randomisées soit 1107 patients recevant une chimiothérapie hautement à moyennement émétisante (dont 561 dans le groupe olanzapine), démontre que l'ajout de l'olanzapine à 5 ou 10 mg versus sétron plus dexaméthasone seuls diminue les NVCI notamment les grades III et IV ; la posologie de 5 mg est moins pourvoyeuse de somnolence et l'efficacité des 2 posologies sur la diminution des NVCI aigus et retardés est comparable (25). Dans les dernières recommandations de l'ASCO, l'olanzapine est associée systématiquement de J1 à J4 dans la prévention des NVCI en cas de chimiothérapie hautement émétisante (26). Dans les recommandations MASCC/ESMO, qui n'ont pas été actualisées depuis 2016, ainsi que dans celles de l'AFSOS actualisées en 2017^G, l'olanzapine reste une option (27).

- **Les autres anti-émétiques :**

- Le niveau d'efficacité des cannabinoïdes (marijuana à usage médical) ne permet pas de les recommander dans le traitement préventif des nausées/vomissements. Leur intérêt est néanmoins croissant (10,28). On rappelle qu'ils ne sont pas autorisés en France dans cette indication.
- Le Lorazepam est un adjuvant utile mais ne doit pas être utilisé seul.

- **Règles hygiéno-diététiques (cf. référentiel AFSOS^G) :**

- Favoriser l'hydratation
- Fractionner l'alimentation : 6 à 8 petits repas/collations /jour
- Privilégier des petits repas froids, éviter les aliments gras/frits/épicés
- Manger lentement
- Boissons selon les goûts du patient entre les repas (eau, infusion, jus de pomme, coca), si besoin avec une tasse fermée et une paille (limitation des odeurs)
- Maintenir une position assise 30 minutes après les repas (à défaut, en décubitus latéral droit)

- **Médecines complémentaires :**

Il n'y a pas d'évidence en faveur ou défaveur des traitements dits complémentaires. L'acupuncture, en complément d'une prophylaxie médicamenteuse bien conduite, pourrait être efficace sur les nausées aiguës sur la base de quelques essais randomisés de petites tailles (29). D'autres essais de plus grande ampleur sont en cours (30–32).

3. Prévention et prise en charge des NVCI

La prévention et le traitement des NVCI sont repris dans les tableaux 5 (chimiothérapies cytotoxiques & immunothérapie) et 6 (thérapies ciblées orales), adaptés des recommandations 2016 du du MASCC/ESMO (27,33) et 2017 de l'ASCO (26,34,35).

^F Hashimoto H, Abe M, Nakao M, Mizutani H, Sakata Y, Fujita Y, Nishimura T, Hirano K, Okada H, Inui N, Sakata Y, Iihara H, Zenda S, Uchitomi Y, Yamaguchi T, Hoshina Y, Yanai T, Iwasa S, Yamamoto N, Ohe Y. A randomized, double-blind, placebo-controlled phase III trial evaluating olanzapine 5 mg combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy: J-FORCE Study. ASCO 2019, #11503

^G AFSOS, Prise En Charge Des Nausées-Vomissements Chimio-Induits, MAJ 15/12/2017, disponible sur <http://www.afsos.org/fiche-referentiel/nausees-vomissements-chimio-induits>, accédé le 08/11/2019

Les différents types de chimiothérapies utilisées dans le traitement des CBNPC sont classés en quatre catégories en fonction de leur risque émétogène : hautement, moyennement, faiblement et minimal (36). Pour chacun de ces risques, un protocole de prévention et de traitement précis est recommandé. Dans les protocoles utilisant plusieurs drogues, il est nécessaire de tenir compte du niveau de la drogue la plus émétisante. Il faut aussi adapter d'emblée le protocole en fonction des facteurs de risque éventuels du patient ; c'est la notion de « **prophylaxie surclassée** » si besoin dès la 1^{ère} cure.

Degré (fréquence)	Molécules	NVCI aiguës		NVCI retardées	
		J1	J2	J3	J4
Hautement émétisantes (>90%)	Cisplatine Cyclophosphamide ≥ 1500 mg/m ²	Aprépitant 125 Sétron ¹ Corticoïde ² (Olanzapine ⁴)	Aprépitant 80 Corticoïde ³ (Olanzapine ⁴)	Aprépitant 80 Corticoïde ³ (Olanzapine ⁴)	Corticoïde ³ (Olanzapine ⁴)
	Cisplatine	Nétupitant + palonosetron (NEPA) Corticoïde ²	Corticoïde ³	Corticoïde ³	Corticoïde ³
	Cyclophosphamide + Anthracycline	Aprépitant 125 Sétron ¹ Corticoïde ² (Olanzapine ⁴)	Aprépitant 80 (Olanzapine ⁴)	Aprépitant 80 (Olanzapine ⁴)	(Olanzapine ⁴)
Moyennement émétisantes (30-90%)	Carboplatine (AUC≥4)	Aprépitant 125 Sétron ¹ Corticoïde ⁴	Aprépitant 80	Aprépitant 80	
	Cyclophosphamide < 1500 mg/m ² Carboplatine AUC<4 Doxorubicine Irinotecan Vinorelbine orale	Sétron ¹ Corticoïde ⁵	(Corticoïde ^{6#})	(Corticoïde ^{6#})	
Faiblement émétisante (10-30%)	Atezolizumab Cetuximab Docetaxel	Corticoïde ^{7*}			
	Etoposide IV et po Gemcitabine Ipilimumab (Nab-)Paclitaxel Pemetrexed Topotecan	OU Sétron ¹ (OU Metoclopramide ⁸)			
Minimale (<10%)	Bevacizumab Bleomycine Nivolumab Pembrolizumab Vincristine Vinorelbine IV	Aucune en l'absence d'ATCD de NVCI			

Tableau 5 – Recommandations concernant le traitement et la prévention des NVCI en fonction du type de chimiothérapie ou immunothérapie administrée (hors thérapies ciblées orales).

- Ondansetron 8mg (0.15mg/kg) IV une fois ou 16mg per os en deux fois ; Granisetron 1mg (0.01mg/kg) IV ou 2mg (option : 1mg) per os en une fois ; Palonosetron 0.25mg IV ou 0.5mg per os une fois.
 - 12 mg de dexaméthasone une fois (soit 80mg de Predniso(lo)ne) en cas d'administration concomitante d'aprépitant ; 20 mg une fois (130mg de Predniso(lo)ne) sinon.
 - 8mg de dexaméthasone une fois (soit 50mg de Predniso(lo)ne) en cas d'utilisation associée à l'aprépitant ; 8mg de dexaméthasone **deux fois par jour** (soit 50mg x 2/j de de Predniso(lo)ne) sinon.
 - 5mg/j - Recommandation ASCO - Option MASCC/ESMO et AFSOS
 - 8mg de dexaméthasone une fois (soit 50mg de Predniso(lo)ne)
 - 8mg de dexaméthasone une fois (soit 50mg de Predniso(lo)ne) bien que 4mg (25mg EP) soit une option.
 - 4 à 8mg de dexaméthasone une fois (25 à 50mg de Predniso(lo)ne).
 - Recommandation MASCC/ESMO - Non figuré dans les recommandations ASCO
- # Recommandé en cas de chimiothérapie à risque de NVCI retardées; en option sinon (MASCC/ESMO et ASCO).
* Option non privilégiée en cas d'immunothérapie

Recommandation

Le choix de la prévention des NVCI repose sur le type de molécules utilisées pour la chimiothérapie et associe les Anti NK1 et/ou les Anti 5HT3 et/ou les corticoïdes et/ou l'olanzapine (hors AMM) et/ou les Anti D2.

Degré (fréquence)	Molécules	Prévention des NVCI
Moyennement émétisantes (30-90%)	Brigatinib [#]	AntiD2 systématiquement associés sur l'ordonnance ; à prendre en cas de besoin.
	Dabrafenib [#] + Trametinib	
	Ceritinib*	
	Crizotinib*	
	Lorlatinib*	
Faiblement émétisante (10-30%)	Afatinib	AntiD2 systématiquement associés sur l'ordonnance ; à prendre en cas de besoin.
	Alectinib	
	Dabrafenib [#]	
	Trametinib	
Minimale (< 10%)	Osimertinib*	
	Gefitinib	
	Erlotinib	

*Les sétrons sont déconseillés en association (allongement du QT).

[#]L'association aux sétrons peut réduire les concentrations plasmatiques du principe actif.

Tableau 6 – Recommandations concernant le traitement et la prévention des NVCI pour les thérapies ciblées orales (d'après (33)).

4. Prise en charge des NVCI anticipées

Les benzodiazépines ont montré un intérêt pour la prévention et le traitement des NVCI anticipées. Toutefois, les traitements comportementaux, et la prévention des NVCI aiguës ou retardées sont également essentiels dans cette indication.

5. Prise en charge des NVCI réfractaires

La définition des NVCI réfractaires n'est pas consensuelle, tout comme leur prise en charge (**Tableau 7**).

Avant de parler de NVCI réfractaires, il est recommandé de s'assurer que la prophylaxie adaptée au risque de chimiothérapie a bien été prescrite et observée.

L'ASCO et l'ESMO/MASCC considèrent l'olanzapine comme l'option thérapeutique de choix pour les patients qui n'en ont pas reçu en prophylaxie. L'olanzapine peut donc être proposée comme un traitement de secours, d'autant plus que sa bonne tolérance et sa simplicité d'administration (1 cp par jour) facilitent la compliance. Une forme lyophilisée a été développée afin d'améliorer la prise (23).

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