UniversitätsKlinikum Heidelberg

Prevention and Management of cancer disease and of chemo-and radiotherapy-induced nausea and vomiting

Focusing on the updated MASCC/ESMO guidelines

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DISCLOSURE SLIDE

Karin Jordan is consultant and/or received Honoraria from:
MSD, Helsinn, Tesaro

….UPDATE OF THE GUIDELINE:

DIFFERENCES?

MAIN DIFFERENCE

2010

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v232–v243, 2010
doi:10.1093/annonc/mdq194

Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference

F. Roila[1], J. Herrstedt[2], M. Aapro[3], R. J. Gralla[4], L. H. Einhorn[5], E. Ballatori[6], E. Bria[7], R. A. Clark-Snow[8], B. T. Espersen[9], P. Feyer[10], S. M. Grunberg[11], P. J. Hesketh[12], K. Jordan[13], M. G. Kris[14], E. Maranzano[15], A. Molassiotis[16], G. Morrow[17], I. Olver[18], B. L. Rapoport[19], C. Rittenberg[20], M. Saito[21], M. Tonato[22] & D. Warr[23]
On behalf of the ESMO/MASCC Guidelines Working Group*

2016

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v119–v133, 2016
doi:10.1093/annonc/mdw270

2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients

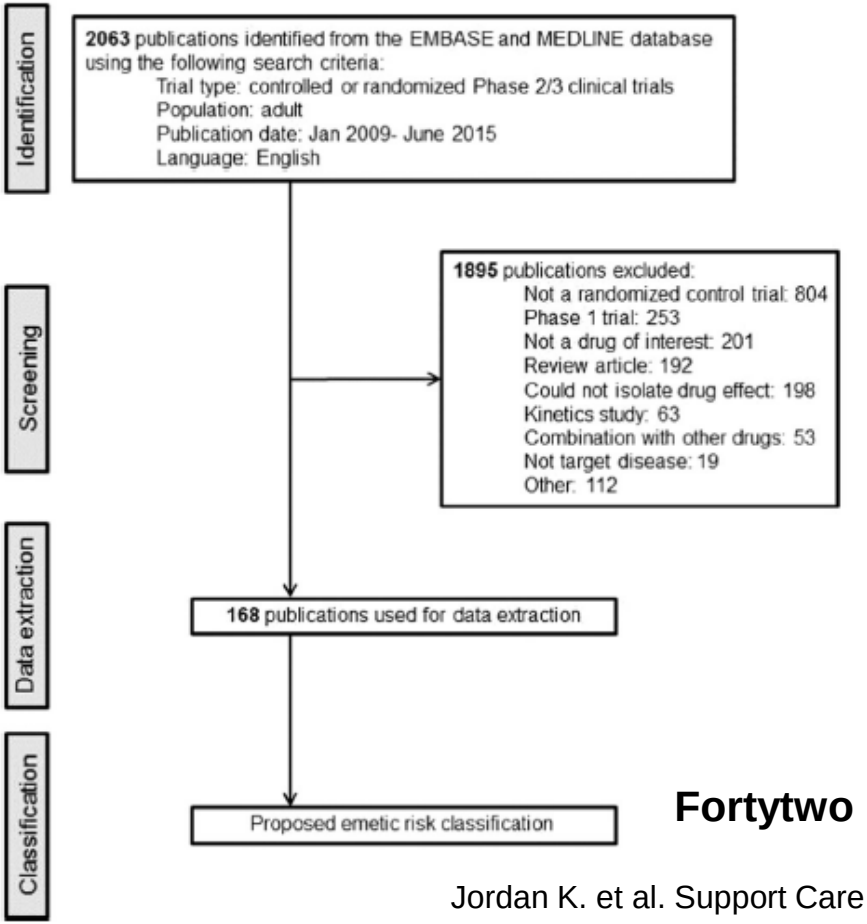
F. Roila[1], A. Molassiotis[2], J. Herrstedt[3], M. Aapro[4], R. J. Gralla[5], E. F[illegible]era[6], R. A. Clark-Snow[7], L. L. Dupuis[8], L. H. Einhorn[9], P. Feyer[10], P. J. Hesketh[11], K. Jorda[illegible], I. Olver[13], B. L. Rapoport[14], J. Roscoe[15], C. H. Ruhlmann[3], D. Walsh[16], D. Warr[17] & M. van d[illegible]Vetering[18] on behalf of the participants of the MASCC/ESMO Consensus Conference Copenhagen 2015*

QUESTIONS, WHICH NEEDED TO BE ADDRESSED FOR THIS UPDATE

- Emetogenic risk classification of new drugs
- Grouping of Anthracycline-cyclophosphamide based chemotherapy: highly emetogenic chemotherapy?
- Individual risk factor adapted prophylactic treatment algorithm?
- Value of the NK1-RA in the moderate and other emetogenic risk settings?
- Value of the atypical neuroleptic Olanzapine: First-line versus rescue?
- Antiemetics in advanced cancer

EMETOGENICITY OF ANTINEOPLASTIC AGENTS

Search algorithm for classifying new antineoplastic agents



Fortytwo new agents identified

Jordan K. et al. Support Care Cancer 2016 [Epub ahead of print]

Update: Important to acknowledge

- Agents are listed now in an alphabetical order.
  The committee member felt that attempting to classifiy the relative emetogenicity of agents within a given level was no longer possible

Table 2 Emetogenic potential of single intravenous antineoplastic agents

HIGH	Anthracycline/cyclophosphamide combination[a]	
	Carmustine	
	Cisplatin	
	Cyclophosphamide ≥ 1500 mg/m^2	
	Dacarbazine	
	Mechlorethamine	
	Streptozocin	
MODERATE	Alemtuzumab	Epirubicin
	Azacitidine	Idarubicin
	Bendamustine	Ifosfamide
	Carboplatin	Irinotecan
	Clofarabine	Oxaliplatin
	Cyclophosphamide < 1500 mg/m^2	Romidepsin
	Cytarabine > 1000 mg/m^2	Temozolomide[b]
	Daunorubicin	Thiotepa[c]
	Doxorubicin	Trabectedin
LOW	Aflibercept	Ipilimumab
	Belinostat	Ixabepilone
	Blinatumomab	Methotrexate
	Bortezomib	Mitomycin
	Brentuximab	Mitoxantrone
	Cabazitaxel	Nab- paclitaxel
	Carfilzomib	Paclitaxel
	Catumaxumab	Panitumumab
	Cetuximab	Pemetrexed
	Cytarabine ≤ 1000 mg/m^2	Pegylated liposomal doxorubicin
	Docetaxel	Pertuzumab
	Eribulin	Temsirolimus
	Etoposide	Topotecan
	5-Fluorouracil	Trastuzumab-emtansine
	Gemcitabine	Vinflunine
MINIMAL	Bevacizumab	Pembrolizumab
	Bleomycin	Pixantrone
	Busulfan	Pralatrexate
	2-Chlorodeoxyadenosine	Rituximab
	Cladribine	Trastuzumab
	Fludarabine	Vinblastine
	Nivolumab	Vincristine
	Ofatumumab	Vinorelbine

[a] The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic.

[b] No direct evidence found for temozolomide IV; as all sources indicate a similar safety profile to the oral formulation, the classification was based on oral temozolomide.

[c] classification refers to individual evidence from pediatric trials

Roila F. et al. Ann Oncol. 2016,27:v119-v133.
Jordan K. et al. Support Care Cancer 2016 [Epub ahead of print]

EMETOGENIC POTENTIAL, ORAL AGENTS*

HIGH	Hexamethylmelamine Procarbazine				
MODERATE	Bosutinib Ceritinib	Crizotinib Cyclophosphamide	Imatinib	Temozolomide	Vinorelbine
LOW	Afatinib Axatinib Capecitabine Dabrafenib Dasatinib	Everolimus Etoposide Fludarabine Ibrutinib Idelalisib	Lapatinib Lenalidomide Olaparib Nilotinib	Pazopanib Ponatinib Regorafenib Sunitinib	Tegafur Uracil Thalidomide Vandetanib Vorinostat
MINIMAL	Chlorambucil Erlotinib Gefitinib	Hydroxyurea Melphalan Methotrexate	L-Phenylalanine mustard Pomalidomide	Ruxolitinib Sorafenib 6-Thioguanine	Vemurafenib Vismodegib

*Classified emetic potential of oral agents based upon a full course of therapy and not a single dose

Roila F. et al. Ann Oncol. 2016,27:v119-v133.
Jordan K. et al. Support Care Cancer 2016 [Epub ahead of print]

CONSIDERING OF INDIVIDUAL RISK FACTORS FOR THE PROPHYLACTIC TREATMENT ALGORITHM?

CONSIDERING OF INDIVIDUAL RISK FACTORS FOR THE PROPHYLACTIC TREATMENT ALGORITHM

- Female Gender
- Young age
- History of chemotherapy
- Anxious personality
- Minimal alcohol use (Caveat ≥5 drinks week is protective)
- History of emesis during pregnancy
- History of motion sickness

Roila F, J Clin Oncol 1991; 4: 675-8, Morrow G, Support Care Cancer 2002; 10: 96-105, Warr D, Support Care Cancer 2010

CONSIDERING OF INDIVIDUAL RISK FACTORS FOR THE PROPHYLACTIC TREATMENT ALGORITHM

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Identifying Cancer Patients at High Risk for Chemotherapy-Induced Nausea and Vomiting (CINV):
The Development of a Prediction Tool
European Society for Medical Oncology
7-11 October 2016
Copenhagen, Denmark
Poster: 1438PD
George Dranitsaris[1], Alex Molassiotis[2], Mark Clemons[1], Eric Roeland[3], Lee Schwartzberg[4], David Warr[5], Karin Jordan[6], Pascale Dielenseger[7], Matti Aapro[8]
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[6]University of Halle, Halle, Germany; [7]Gustave Roussy Cancer Campus, Villejuif, France; [8] IMO Clinique de Genolier, Genolier, Switzerland

Roila F, J Clin Oncol 1991; 4: 675-8, Morrow G, Support Care Cancer 2002; 10: 96-105, Warr D, Support Care Cancer 2010

ANTIEMETIC DRUGS

Recommended Doses of Serotonin Receptor (5-HT_3) Antagonists for Acute Nausea and Vomiting

AGENT	ROUTE	ANTIEMETICS
Ondansetron	IV	8 mg or 0.15 mg/Kg
	Oral	16 mg*
Granisetron	IV	1 mg or 0.01 mg/Kg
	Oral	2 mg (or 1 mg**)
Dolasetron	Oral	100 mg
Tropisetron	IV	5 mg
	Oral	5 mg
Palonosetron	IV	0.25 mg
	Oral	0.5 mg

* Randomized studies have tested the 8 mg twice daily schedule.
** The 1 mg dose is preferred by some panelists.

Recommended Corticosteroid* (Dexamethasone) Dosing

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

** The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

Recommended NK_1 Receptor Antagonist Dosing

NK_1 Receptor Antagonist	Dose and Schedule
APREPITANT* and FOSAPREPITANT - Acute Emesis	Aprepitant: 125 mg once on the day of chemotherapy* ***- or -*** Fosaprepitant: 150 mg IV, once on the day of chemotherapy
APREPITANT* and FOSAPREPITANT - Delayed Emesis	Aprepitant 80 mg orally, once daily for the 2 days after chemotherapy; or none if Fosaprepitant is used
ROLAPITANT	180 mg orally once on the day of chemotherapy
NETUPITANT	300 mg netupitant/0.5 mg palonosetron orally once on the day of chemotherapy

* aprepitant 165 mg as a single dose before chemotherapy (and none day 2-3) is registered by EMA and other authorities

PROPHYLACTIC RECOMMENDATIONS

Most important 2 slides of this presentation and do not forget as …

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**5-HT$_3$** + **DEX** + **NK$_1$**
High AC	**5-HT$_3$** + **DEX** + **NK$_1$**
Carboplatin	**5-HT$_3$** + **DEX** + **NK$_1$**
Moderate (other than carboplatin)	**5-HT$_3$** + **DEX**
Low	**5-HT$_3$** or **DEX** or **DOP**
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA

DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, Palonosetron is the preferred 5-HT$_3$ receptor antagonist.

DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**DEX** or (if APR 125mg for acute: (**MCP** + **DEX**) or **APR**)
High AC	None or (if APR 125mg for acute: **DEX** or **APR**)
Carboplatin	None or (if APR 125mg for acute: **APR**)
Oxaliplatin, or Anthracycline, or Cyclophosphamide	**DEX** can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE | **MCP** = METOCLOPRAMIDE | **APR** = APREPITANT

OLANZAPINE

COMMITTEE II (5/5):

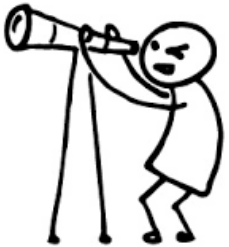
The MASCC/ESMO Antiemetics Guidelines Committee has discussed the presently available published data about olanzapine, which suggest that it is an effective antiemetic agent.

Olanzapine may be considered with a 5-HT_3 receptor antagonist plus dexamethasone, particularly when nausea is an issue.

(**NOTE**: Patient sedation may be a concern for the 10 mg dose.)

MASCC Level of Confidence : Low
MASCC Level of Consensus: Low
ESMO Level of Evidence: II
ESMO Grade of Recommendation: B

EMERGING DATA AFTER THE GUIDELINE PUBLICATION



OLANZAPINE IN HIGHLY EMETOGENIC CHEMOTHERAPY

All patients received triple antiemetic regimen: **5-HT$_3$** = serotonin$_3$ receptor antagonist | **NK$_1$** = neurokinin$_1$ receptor antagonist | DEXA-METHASONE

	Olanzapin-Group (N = 192)	Placebo-Group (N = 188)	P-value
Nausea 0-120 hr after CTX	62.7 %	78.1 %	0.002

Increased sedation on day 2 (5 % severe) in Olanzapin-Group

Conclusion: Increased efficacy with a 4 drug regimen including Olanzapin…but 4 drugs to manage 1 side effect?

Navari RM. et al., N Engl J Med. 2016;375:134-42

MODERATELY EMETOGENIC CHEMOTHERAPY

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**5-HT$_3$** + **DEX** + **NK$_1$**
High AC	**5-HT$_3$** + **DEX** + **NK$_1$**
Carboplatin	**5-HT$_3$** + **DEX** + **NK$_1$**
Moderate (other than carboplatin)	**5-HT$_3$** + **DEX**
Low	**5-HT$_3$** or **DEX** or **DOP**
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK$_1$ = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA

DOP = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, Palonosetron is the preferred 5-HT$_3$ receptor antagonist.

Risk of emesis	Intravenous antineoplastig agents		
MODERATE (30-90 %)	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500 mg/m²	Cytarabine > 1000 mg/m² Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide	Irinotecan Oxaliplatin Romidepsin Temozolomide Thiotepa Trabectedin

EVIDENCE FOR CARBOPLATIN BASED CHEMOTHERAPY

NK1-RA Regimens: Carboplatin-based regimens

	Overall (0-120 h) No Emesis Rate	NK1 RA+ 5-HT3 RA + DEX	5-HT3 RA + DEX	Absolute Difference
APR	Gralla (N = 192)[a] J ClinOncol 2010	84 %	70 %	14 %
	Overall (0-120 h) Complete Response	**NK1RA + 5-HT3 RA + DEX**	**5-HT3 RA + DEX**	**Absolute Difference**
	Tanioka (N = 91) BrJCancer 2013	62 %	52 %	10 %
	Ito (N = 134) LungCancer 2014	80 %	67 %	14 %
	Yahata (N = 324) Int J Clin Oncol 2015	62 %	47 %	15 %
ROL	Hesketh (N = 401) [b] Cancer 2016	80 %	65 %	15 %
FOSAPR	Weinstein (N=513) [c] ESMO 2016	78%	63%	15%
NEPA/ APR	Jordan (N= 196)[d] J Support Care Cancer 2016	NEPA+Dex	Apr+Pal+Dex	
		80%	82%	

[a] Posthoc analysis Rapaport 2010; [b] Posthoc analysis Schwartzberg 2015,
[c] Posthoc analysis Weinstein Study 2016 [d] Posthoc analysis Gralla 2014

Jordan K et al, AnnOncol 2015; 26:1081-90

Pure MEC data, without carboplatin

Drug	Post hoc analysis	Patients	Δ CR overall phase	Remarks
Fosapr	Weinstein ESMO 2016*	487	6%	Abstract
Rolapitant	Hesketh ASCO 2015**	228	13%	Abstract
Drug	**Rrandomized controlled trial**	**Patients**	**Δ CR overall phase**	**Remarks**
Casopitant	Hesketh 2012	707	1%	Purely oxaliplatin-based
Apr/Fosapr	Nishimura 2015	370	11%	Purely oxaliplatin-based

* Post hoc analysis of: Weinstein C. AnnOncol 2016;27:172-78

** Post hoc analysis of: Schwartzberg L. Lancet 2015; 9:1071-8

HIGH DOSE CHEMOTHERAPY

COMMITTEE V (2/3):

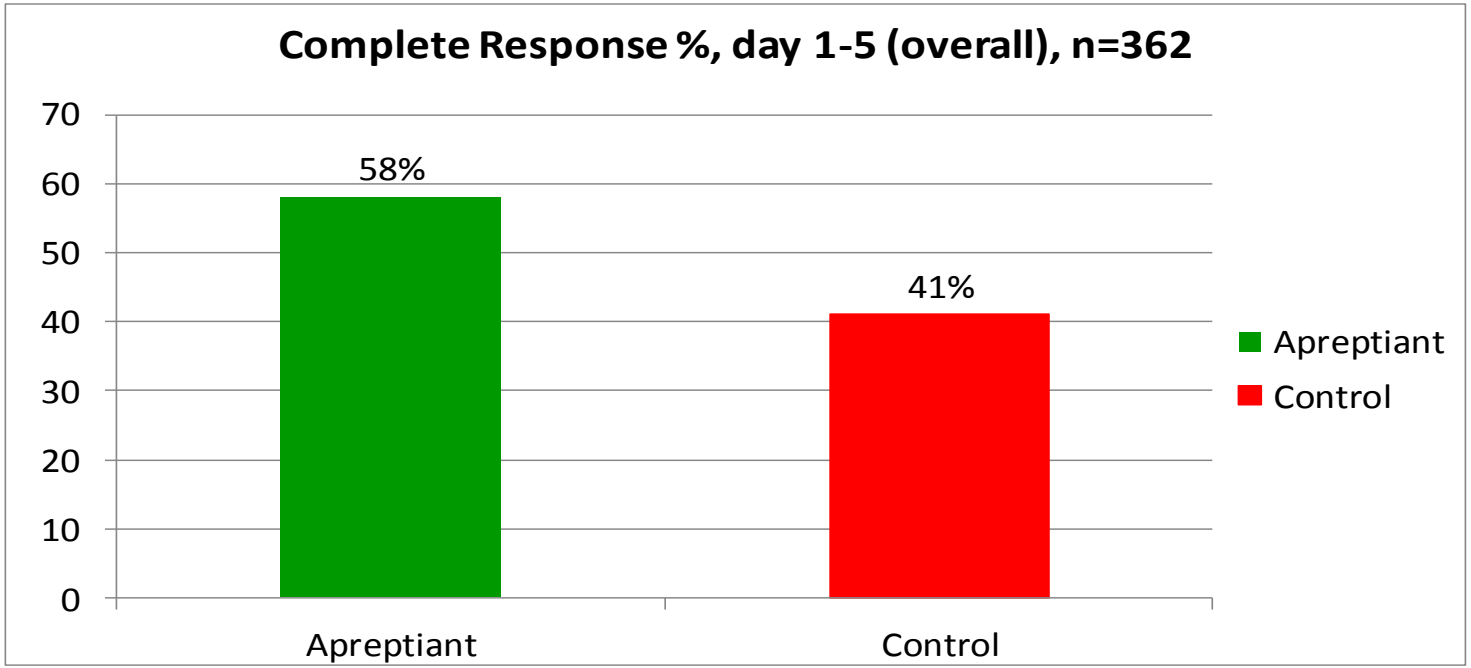
Prevention of Nausea and Vomiting in Patients Receiving High-Dose Chemotherapy

For patients receiving high-dose chemotherapy for stem cell transplant, a combination of a 5-HT_3 receptor antagonist with dexamethasone and aprepitant (125 mg orally on day 1 and 80 mg orally on days 2 to 4) is recommended before chemotherapy.

MASCC Level of Confidence: High
MASCC Level of Consensus: High
ESMO Level of Evidence: I
ESMO Grade of Recommendation: A

HIGH DOSE-CHEMOTHERAPY

With high dose Melphalan



CR: no vomiting, no rescue therapy

Schmitt T. JCO 2014

MULTIPILE DAY CISPLATIN

COMMITTEE V (1/3):

Prevention of Nausea and Vomiting in Patients Receiving Multiple-Day Cisplatin

Patients receiving multiple-day cisplatin should receive a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting.

MASCC Level of Confidence: Moderate

MASCC Level of Consensus: Moderate

ESMO Level of Evidence: II

ESMO Grade of Recommendation: B

NOTE: The 5-HT_3 receptor antagonists should be dosed at day 1-5, except for palonosetron, which should be dosed on days 1, 3, and 5 only.

BREAKTHROUGH NAUSEA AND VOMITING

COMMITTEE V (3/3):

Guideline for Breakthrough Nausea and Vomiting

The available evidence for breakthrough nausea and vomiting suggests the use of 10 mg oral olanzapine, daily for 3 days.

(The mild to moderate sedation in this patient population, especially elderly patients, is a potential problem with olanzapine.)

MASCC Level of Confidence: Moderate

MASCC Level of Consensus: Moderate

ESMO Level of Evidence: II

ESMO Grade of Recommendation: B

NOTE: No guideline was felt to be appropriate for refractory nausea and vomiting.

RADIOTHERAPY INDUCED NAUSEA AND VOMITING (RINV)

Committee VII (1/5): Levels of Emetic Risk with Radiation Therapy

RISK LEVEL*	AREA OF TREATMENT
HIGH	Total body irradiation
MODERATE	Upper abdomen, craniospinal
LOW	Cranium, head & neck, thorax region, pelvis
MINIMAL	Extremities, breast

* in concomitant radiochemotherapy, the antiemetic prophylaxis is according to the chemotherapy-related antiemetic guidelines of the corresponding risk category, unless the risk of nausea and vomiting is higher with radiotherapy than with chemotherapy.

COMMITTEE VII (2/5):

Prevention of Nausea and Vomiting in Patients Receiving Highly Emetic Radiation Therapy: Total Body Irradiation

Patients receiving highly emetic radiation therapy should receive a 5-HT_3 receptor antagonist plus dexamethasone.

MASCC Level of Confidence: High

(For the addition of dexamethasone: Moderate)

MASCC Level of Consensus: High

ESMO Level of Evidence: II

(For the addition of dexamethasone: III)

ESMO Grade of Recommendation: B

(For the addition of dexamethasone: C)

COMMITTEE VII (3/5):

Prevention of Nausea and Vomiting in Patients Receiving Moderately Emetic Radiation Therapy: Upper Abdomen, Craniospinal

Patients receiving moderately emetic radiation therapy should receive a 5-HT_3 receptor antagonist and optional short-course dexamethasone.

MASCC Level of Confidence: High

(For the addition of dexamethasone: Moderate)

MASCC Level of Consensus: High

ESMO Level of Evidence: II

ESMO Grade of Recommendation: A

(For the addition of dexamethasone: B)

COMMITTEE VII (4/5):

Prevention of Nausea and Vomiting in Patients Receiving Low Emetic Radiation Therapy: Cranium, Head & Neck, Thorax Region, Pelvis

Patients receiving low emetic radiation therapy should receive prophylaxis or rescue with a 5-HT_3 receptor antagonist.

MASCC Level of Confidence: Moderate
(For rescue: Low)

MASCC Level of Consensus: High

ESMO Level of Evidence: III
(For Rescue: IV)

ESMO grade of recommendation: B
(For Rescue: C)

COMMITTEE VII (5/5):

Guideline for the Prevention of Nausea and Vomiting in Patients Receiving Minimal Emetic Radiation Therapy: Extremities, Breast

Patients receiving minimally emetic radiation therapy should receive rescue with a dopamine receptor-antagonist or a 5-HT_3 receptor antagonist.

MASCC Level of Confidence: Low
MASCC Level of Consensus: High
ESMO Level of Evidence: IV
ESMO Grade of Recommendation: D

ANTIEMETICS IN ADVANCED CANCER

ANTIEMETICS IN ADVANCED CANCER

In summary

- The antiemetic drug of choice in advanced cancer is **metoclopramide** (titrated to effect).
  - Alternative options include haloperidol, levomepromazine or olanzapine.
  - The use of cyclizine or 5-HT_3 receptor antagonists is poorly defined to date and may be used when dopamine antagonists are contraindicated or ineffective.

ANTIEMETICS IN ADVANCED CANCER: BOWEL OBSTRUCTION

In summary

- The drug recommended in bowel obstruction is **octreotide**, dosed around the clock, and given alongside a conventional antiemetic (with the committee recommending haloperidol).
- If octreotide plus antiemetic is suboptimal, the use of **anticholinergic anti-secretory agents** (e.g. scopolamine butylbromide, glycopyrronium bromide) and/or **corticosteroids** is recommended as either adjunct / alternative interventions.
- The use of cyclizine* or $5HT_3$ receptor antagonists is poorly defined in this setting**. Metoclopramide should be used with caution in partial bowel obstruction and should not be used in complete bowel obstruction.

* Unavailable in some countries.

** Caution should be exercised because of the risk of drug interactions.

COMMITTEE IX (3/3): Advanced Cancer

Treatment of Nausea and Vomiting in Advanced Cancer: Opioid-induced Emesis

No recommendation can be made about specific antiemetics, although various antiemetics may help. Opioid rotation and route switching may be effective approaches. There is no data to support prophylactic antiemetics in this situation.

MASCC Level of Consensus: High
MASCC Level of Confidence: Low
ESMO Level of Evidence: V
ESMO Grade of Recommendation: D

FURTHER READING

Online slides: www.mascc.org

Full publication: http://annonc.oxfordjournals.org/content/27/suppl_5.toc

And: http://link.springer.com/journal/520

MASCC/ESMO ANTIEMETIC GUIDELINE 2016