PREVENTION AND MANAGEMENT OF CHEMO-AND RADIOTHERAPY-INDUCED NAUSEA AND VOMITING

Focusing on the updated MASCC/ESMO guidelines

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DISCLOSURE OF INTEREST

Prof. Dr. Karin Jordan

- **Personal financial interests, honoraria for speaker, consultancy or advisory role, royalties, direct research funding**: MSD, Merck, Amgen, Hexal, Riemser, Helsinn, Tesaro, Kreussler, Voluntis, Pfizer, Pommemed, Pharma Mar, Prime Oncology, OnkoUpdate, Annals of Oncology, UpToDate
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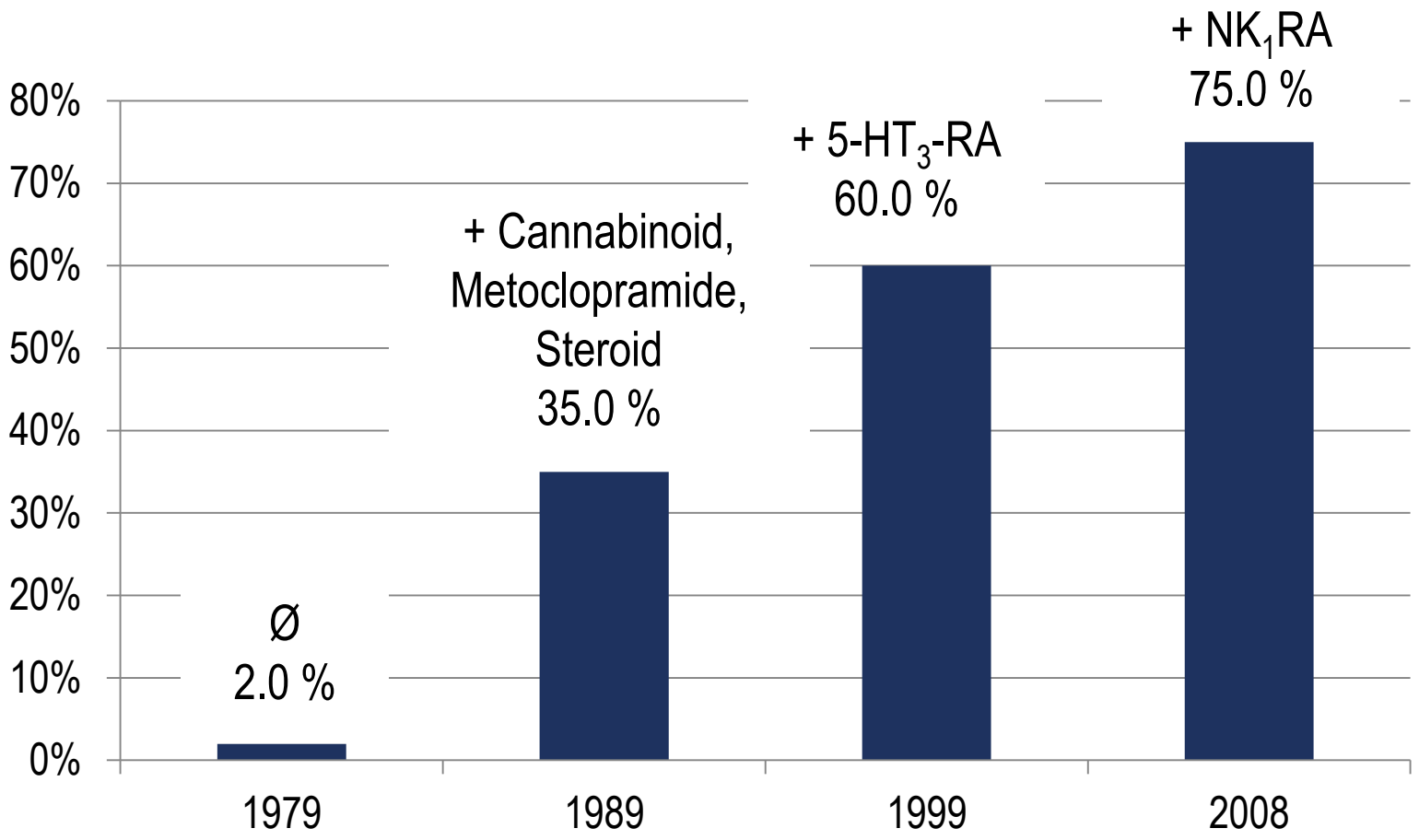
PROGRESS WE MADE OVER THE YEARS

CHEMOTHERAPY-INDUCED EMESIS RESPONSE RATES (%)

Cisplatin (highly emetogenic)



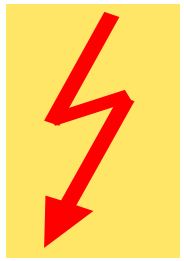
5-HT_3	Receptor Antagonist
NK_1	Neurokinin 1
RA	receptor antagonist

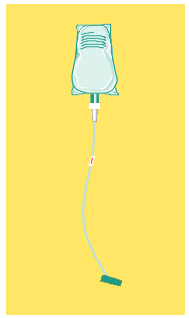
Hesketh PJ. N Engl J Med 2008;358:2482–94.

PATHOPHYSIOLOGY OF EMESIS

TIME COURSE OF CANCER THERAPY INDUCED EMESIS

Therapy





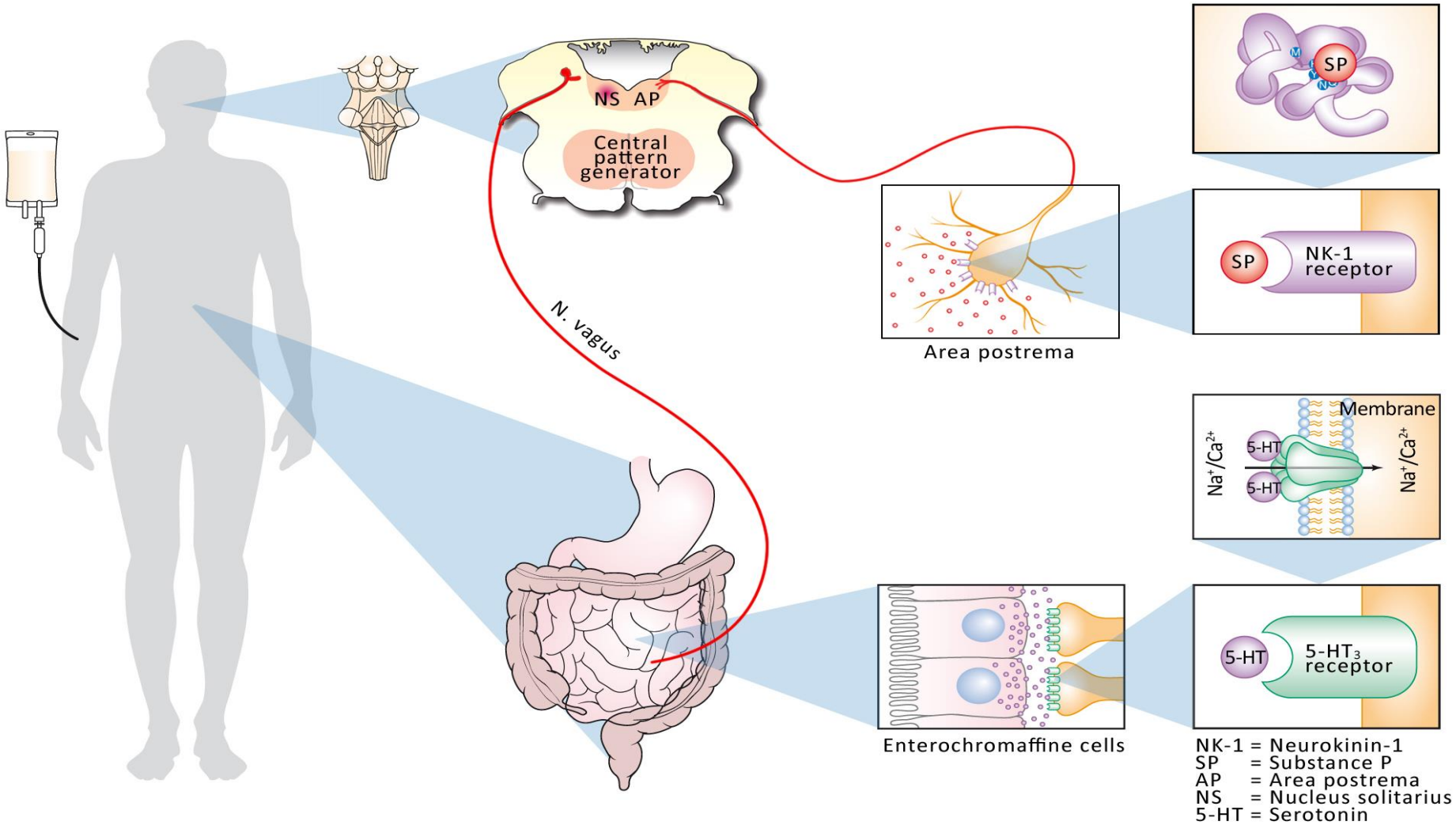
Acute Emesis
24 h after Therapy

Delayed Emesis
2-5 days after therapy

Serotonin/
5-HT_3 RAs

Substance P /
NK_1-Antagonist

RELEVANCE OF SEROTONIN AND SUBSTANCE P



Modified: Jordan K, Supportive Oncology 2010

ANTIEMETIC GUIDELINES

INTERNATIONAL GUIDELINES FOR ANTIEMETIC TREATMENT

Antiemetic Risk Groups

Antiemetic risk groups[1-3]	
Emetic risk group	**% pts**
High emetic risk	90 % or more of patients experience acute emesis
Moderate emetic risk	30 % to 90 % of patients experience acute emesis
Low emetic risk	10 % to 30 % of patients experience acute emesis
Minimal emetic risk	fewer than 10 % of patients experience acute emesis

1. Roila F. et al. Ann Oncol. 2016 Sep;27(suppl 5):v119-v133. MASCC/ESMO Antiemetic Guideline 2016 V.1.2. Available at: http://www.mascc.org/;
2. NCCN: National Comprehensive Cancer Network; NCCN Clinical Practice Guidelines in Oncology; Version 1.2018. Available at: www.nccn.org
3. Hesketh P. J. et al. J Clin Oncol. 2017 Oct 1;35(28):3240-3261. doi: 10.1200/JCO.2017.74.4789. Epub 2017 Jul 31.

EMETOGENIC RISK OF I.V. AGENTS

High (> 90 %)	Cisplatin, Streptozocin, Carmustin, Dacarbazin, Antrazyclin/Cyclophosphamid based regimen, Cyclophosphamid ≥ 1500 mg/m^2, Mechlorethamin
Moderate (30-90 %)	Alemtuzumab, Arsentrioxide, Azacitidin, Bendamustin, Carboplatin, Clofarabin, Cyclophosphamid < 1500 mg/m^2, Cytarabin > 1000 mg/m^2, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Ifosfamid, Interferon α, Irirnotecan, Oxaliplatin, Romidepsin, Temozolomid, Thiotepa, Trabectidin
Low (10-30 %)	Aflibercept, Asparaginsäure, Belinostat, Blinatumomab, Bortezomib, Brentuximab, Cabazitaxel, Cetuximab, Cytarabin < 1000 mg/m^2, Dactinomycin, Docetaxel, Doxorubicin (liposomalpegyliert), Eribulin, Etopsid, 5-Fluorouracil, Gemcitabin, Ipilimumab, Methotrexat, Mitomycin, Nab-Paclitaxel, Paclitaxel, Panitumumab, Pemetrexed, Pertuzumab, Topotecan
Minimal (< 10 %)	Bevacizumab, Bleomycin, Buserelin, Busulfan, 2- Chlordeoxyadenosin, Cladribin, Fludarabin, Fulvestrant, Goserelin, Leuprorelin, Nivolumab, Pembrolizumab, Rituximab, Trastuzumab, Vinblastin, Vincristin, Vinorelbin

Roila F. et al. Ann Oncol. 2016,27:v119-v133.
Jordan K. et al. Support Care Cancer 2017

EMETOGENIC RISK OF ORAL AGENTS

High (> 90 %)	Hexamethylmelamine, Procarbazine
Moderate (30-90 %)	Bosutinib, Ceritinib, Crizotinib, Cyclophosphamide, Imatinib, Temozolomide, Vinorelbine
Low (10-30 %)	Afatinib, Axatinib, Capecitabine, Dabrafenib, Dasatinib, Everolimus, Etoposide, Fludarabine, Ibrutinib, Idelalisib, Lapatinib,, Lenalidomide, Olaparib, Nilotinib, Pazopanib, Ponatinib, Regorafenib, Sunitinib, Tegafur Uracil, Thalidomide Vandetanib, Vorinostat
Minimal (< 10 %)	Chlorambucil, Erlotinib, Gefitinib, Hydroxyurea, Melphalan, Methotrexate, Pomalidomide, Ruxolitinib, Sorafenib, 6-Thioguanine, Vemurafenib, Vismodegib

Roila F. et al. Ann Oncol. 2016,27:v119-v133.
Jordan K. et al. Support Care Cancer 2017

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?

- Female Gender
- Young age
- History of chemotherapy
- Anxious personal
- Minimal drinks week is protective)
- g pregnancy
- ion sickness

Not yet relevant in the guidelines but this may change in the future

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

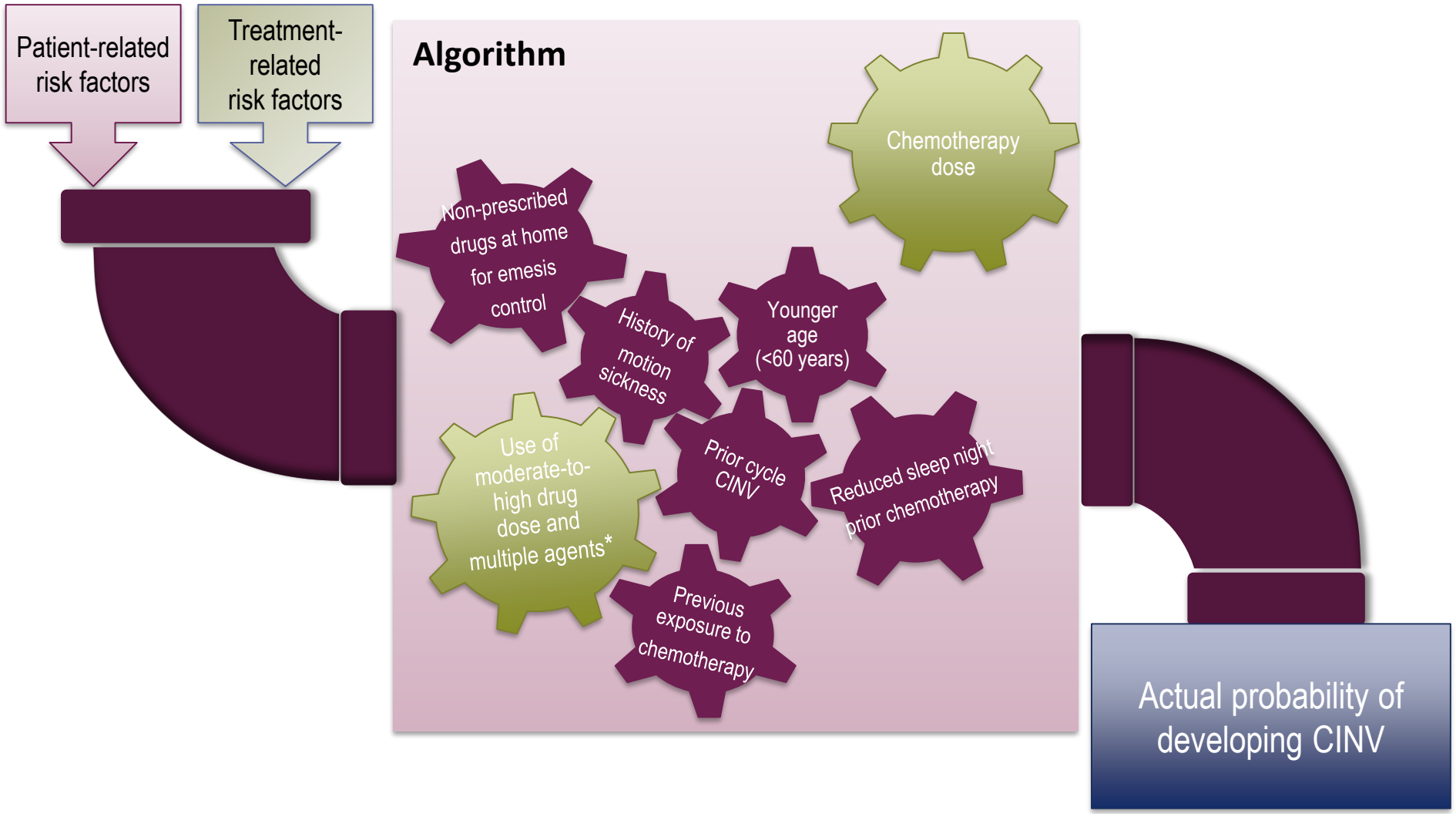
Annals of Oncology 00: 1–8, 2017
doi:10.1093/annonc/mdx100
Published online 7 April 2017

ORIGINAL ARTICLE

The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting

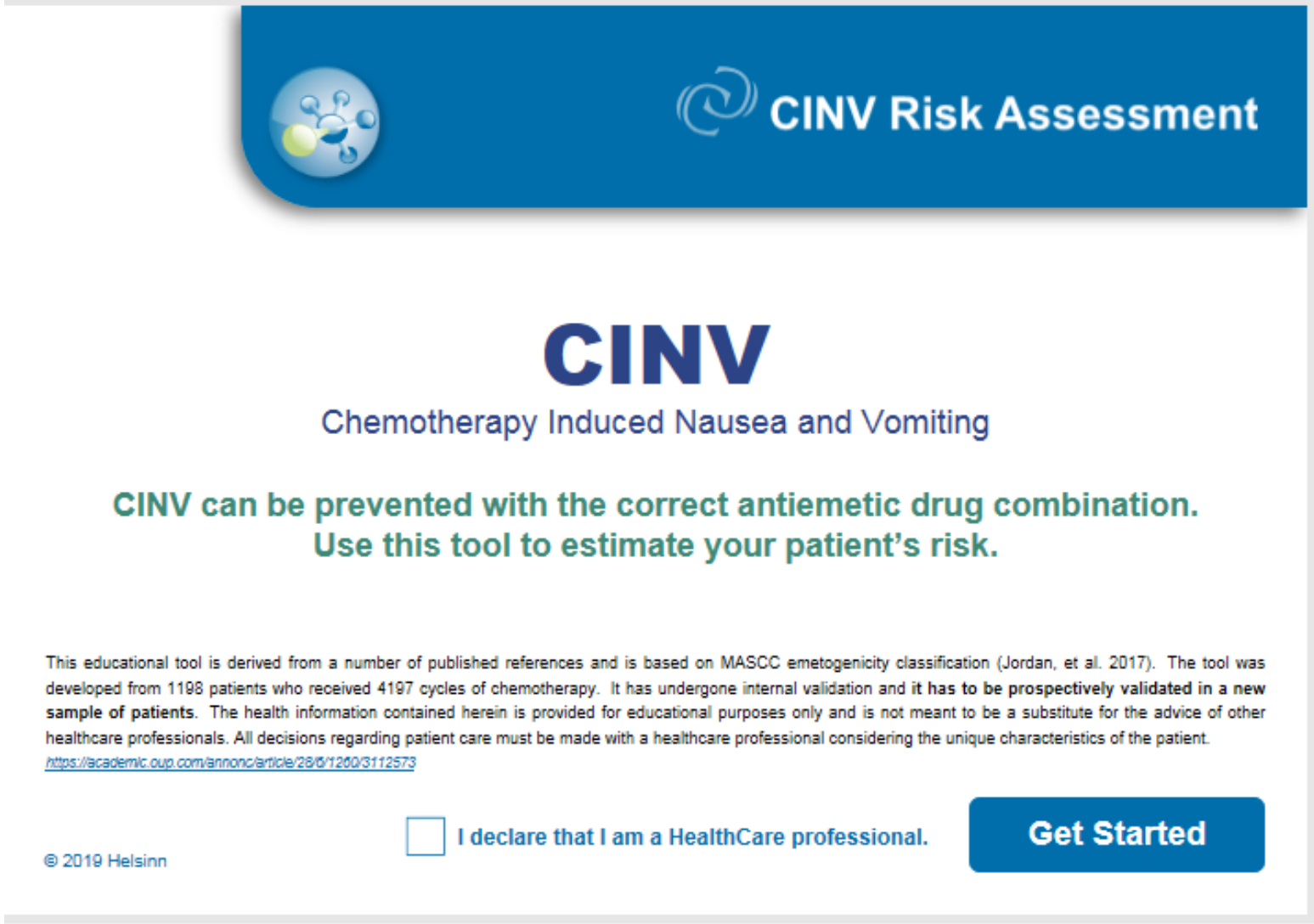
G. Dranitsaris[1*], A. Molassiotis[2], M. Clemons[1], E. Roeland[3], L. Schwartzberg[4], P. Dielenseger[5], K. Jordan[6], A. Young[7] & M. Aapro[8]

PREDICTION TOOL



http://www.riskcinv.org/

PREDICTION TOOL



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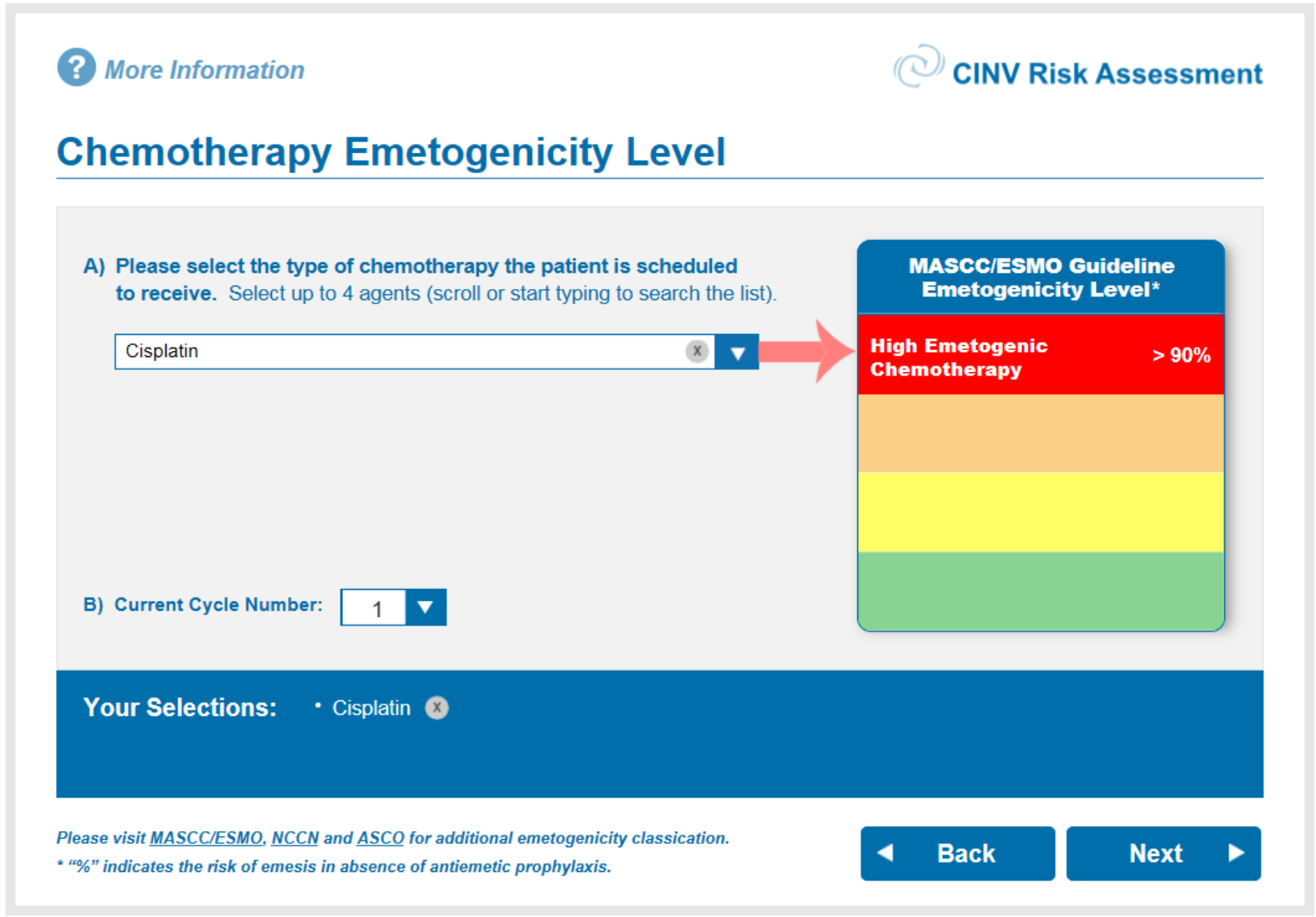

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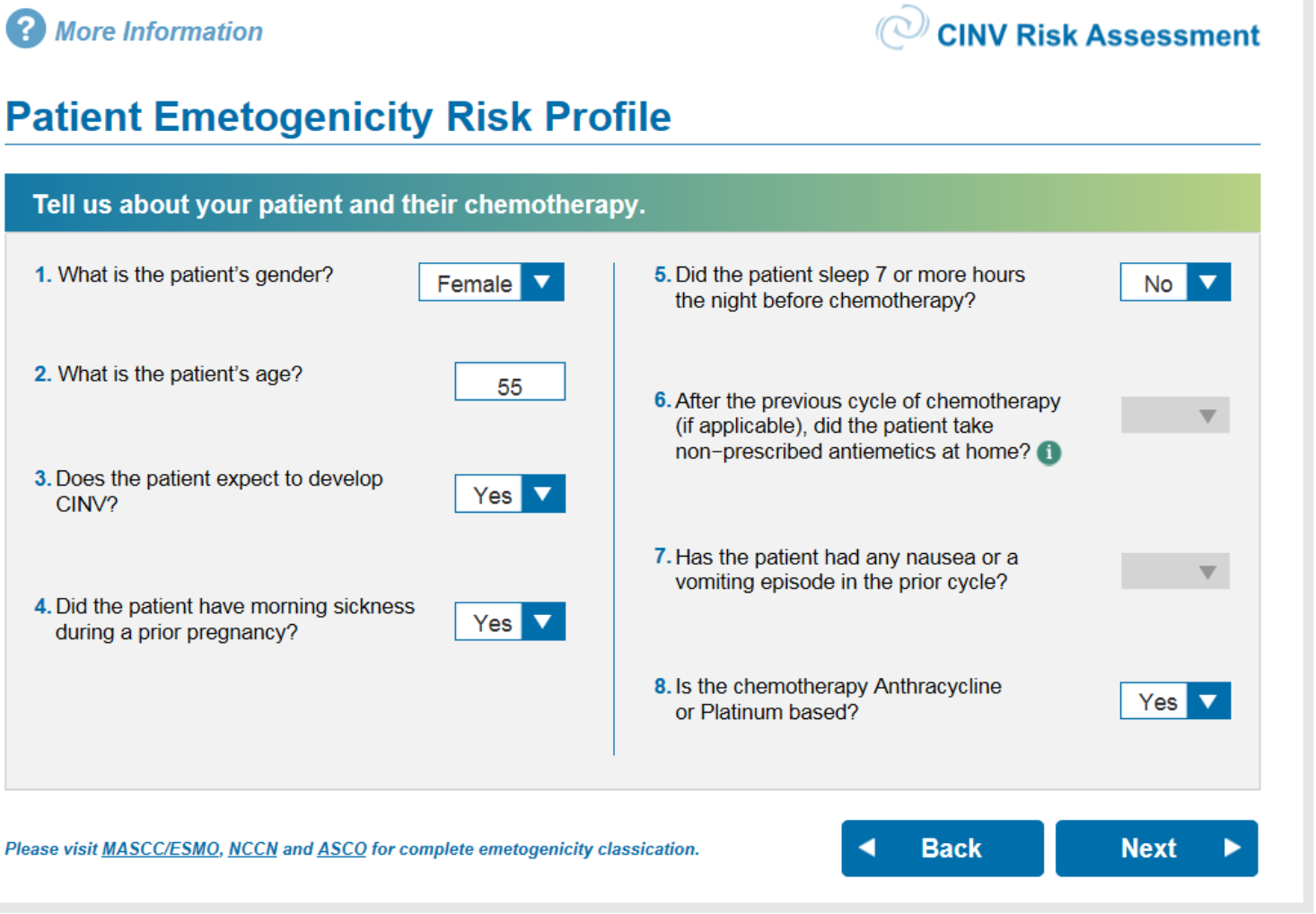

http://www.riskcinv.org/

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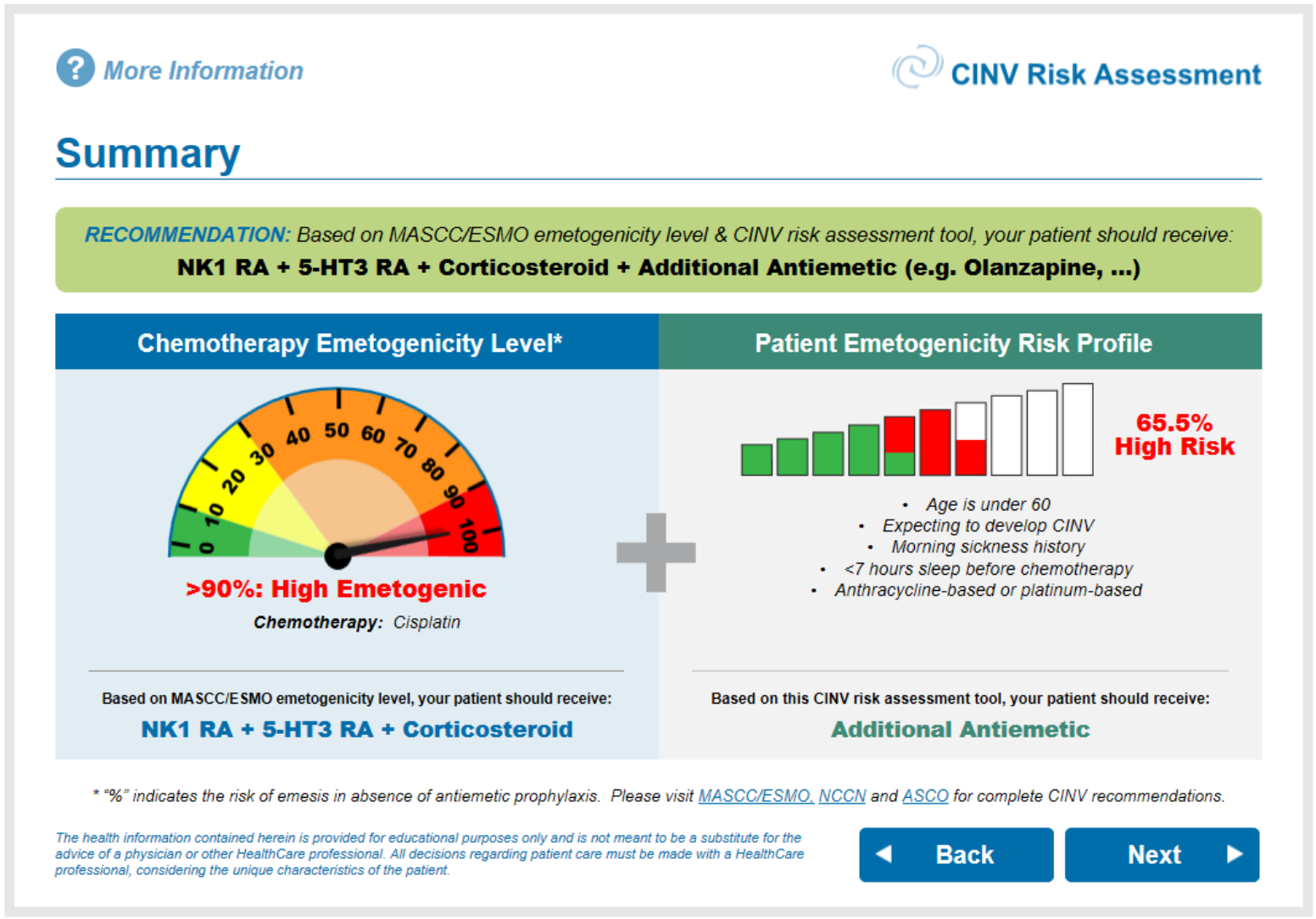

http://www.riskcinv.org/

ANTIEMETIC DRUGS

ANTIEMETIC DRUGS

		Antiemetic efficacy of treatments	
Mode of action	**Class**	**Acute emesis**	**Delayed emesis**
5-HT_3 receptor	5-HT_3 antagonists (ondansetron, palonosetron)	++	+/- +/- +
NK_1 receptor	NK_1 antagonists (aprepitant, fosaprepitant)	+	++
Multiple	Steroids	+(+)	+(+)
DA D_2 receptor	Metoclopramide	(+)	(+)
GABA-chloride channel complex	Benzodiazepines	(+)	(+)
DA D_2 receptor Multiple receptors	Classical Neuroleptics Olanzapine	(+) +	(+) +
CB1-Rezeptor	Cannabinoids	(+)	(+)
Muscarinic/ cholinergic rec.	Antihistamines	–	–

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.

PRINCIPLES OF ANTIEMETIC THERAPY

5-HT_3 receptor antagonists

Lowest fully effective dose should be used

- Once all relevant receptors are saturated, higher doses do not enhance any aspect of activity

Once daily is enough

- Single dose is as active as multiple-dose regimens

Oral is good enough

- Oral agents are as effective as intravenous antiemetics
- Bioavailability is between 50-80%

MASCC 2009, Kris 2006

ESMO

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

CURRENT ASCO GUIDELINES

	Acute Emesis (< 24h)	→	Delayed Emesis (> 24h)
High = Cisplatin and AC-based **> 90 %**	5-HT_3-RA + Dex. 12 mg + NK_1-RA + Olanzapin 10 mg	→	Dex. 8 mg 2x tgl. + Olanzapin 10 mg Tag 2-4+ Aprepitant 80 mg Tag 2-3 (if Aprepitant was the selected NK_1-RA)
Carboplatin	5-HT_3-RA + Dex. 8 mg + NK_1-RA	→	No treatment Or if administration of Aprepitant on day 1 then administration of Aprepitant on days 2-3
Moderate **30 – 90 %**	5-HT_3-RA + Dex. 8 mg	→	Dex. 8 mg 1x tgl. Only at e.g. Cyclophosphamid, Doxorubicin, Oxaliplatin
Low **10 – 30 %**	Monotherapy: Dex. 8 mg or 5-HT_3-RA	→	No treatment
Minimal **< 10 %**	No treatment	→	No treatment

Hesketh, PJ, J Clin Oncol, 2017; 35:3240-3261

OLANZAPINE IN HIGHLY EMETOGENIC CHEMOTHERAPY

All patients received triple antiemetic regimen:

$5\text{-}HT_3$ = 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

ESMO

MODERATELY EMETOGENIC CHEMOTHERAPY

focus

EVIDENCE FOR CARBOPLATIN-BASED CHEMOTHERAPY

NK_1-RA REGIMENS: CARBOPLATIN-BASED REGIMENS

	Overall (0-120 h) No Emesis Rate	NK_1 RA+ $5\text{-}HT_3$ RA + DEX	$5\text{-}HT_3$ RA + DEX	Absolute Difference
APR	Gralla (N = 192)[a] J ClinOncol 2010	84 %	70 %	14 %
	Overall (0-120 h) Complete Response	**NK_1RA + $5\text{-}HT_3$ RA + DEX**	**$5\text{-}HT_3$ 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

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)

RADIOTHERAPY-INDUCED NAUSEA AND VOMITING

Emetic Risk level	Area of treatment	Antiemetic recommendation
High	Total body irradiation	Prophylaxis with 5-HT_3-RA + DEX
Moderate	Upper abdomen, craniospinal	Prophylaxis with 5-HT_3-RA + optional DEX
Low	Cranium,	Prophylaxis or rescue with DEX
	Head and neck, thorax region, pelvis	Prophylaxis or rescue with DEX, a dopamine RA, or a 5-HT_3-RA
Minimal	Extremities, breast	Rescue with DEX, a dopamine RA, or a 5-HT_3-RA

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

ACUTE NAUSEA AND VOMITING: SUMMARY

Emetic Risk Group	Antiemetics						
High Non-AC	5-HT_3	+	DEX	+	NK1	+	(OLA)*
High AC	5-HT_3	+	DEX	+	NK1	+	(OLA)*
Carboplatin	5-HT_3	+	DEX	+	NK1		
Moderate (Other than Carboplatin)	5-HT_3	+	DEX				
Low	5-HT_3	or	DEX	or	DOP		
Minimal	No routine prophylaxis						