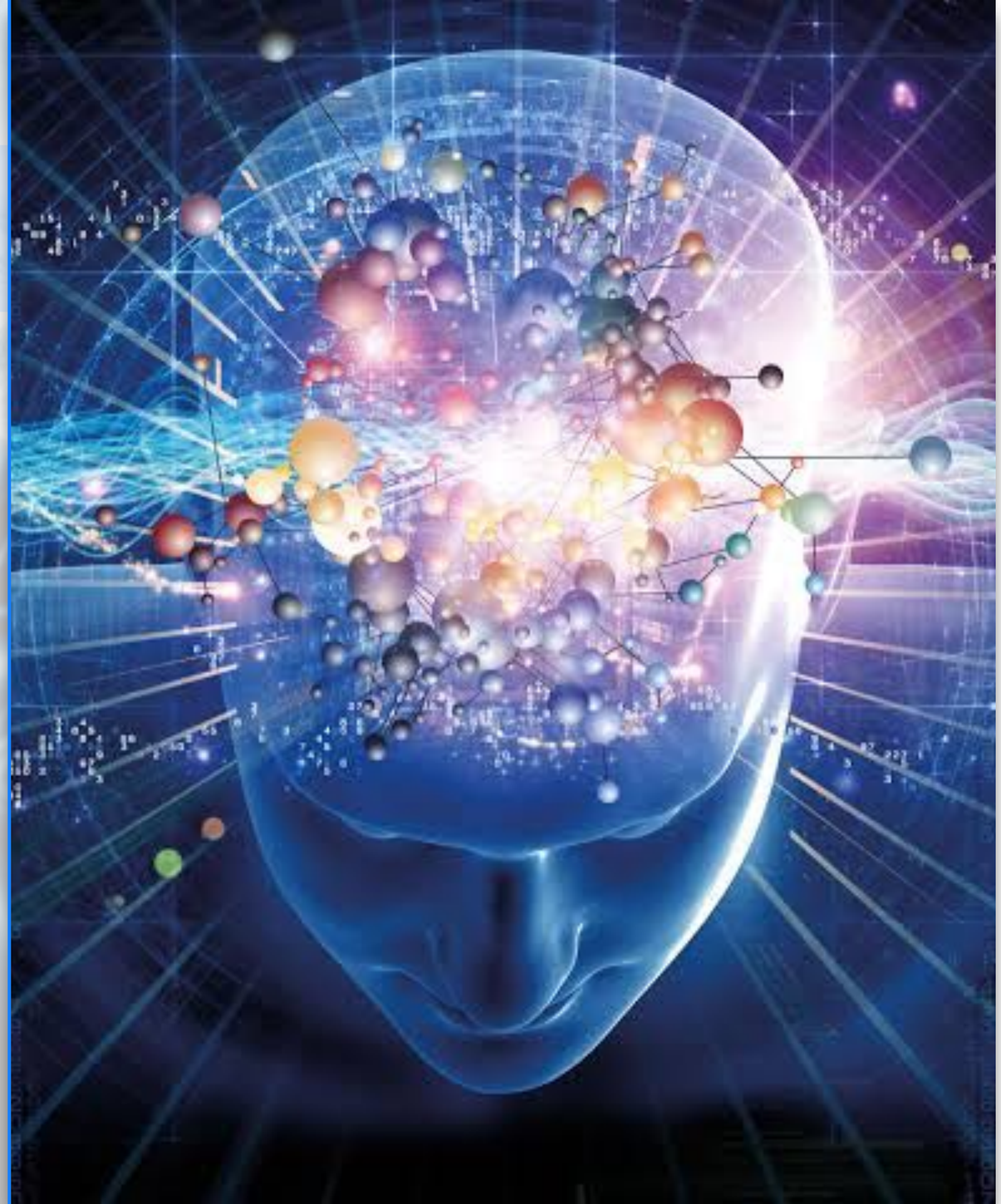
12th Clinical Oncology Pharmacy Symposium 2019:
"Myth and fact in oncology"



Debate issues focus on supportive care

Olanzapine *VS* NK$_1$RA base regimen

อ.ภก.สุธาร จันทะวงศ์

คณะเภสัชศาสตร์

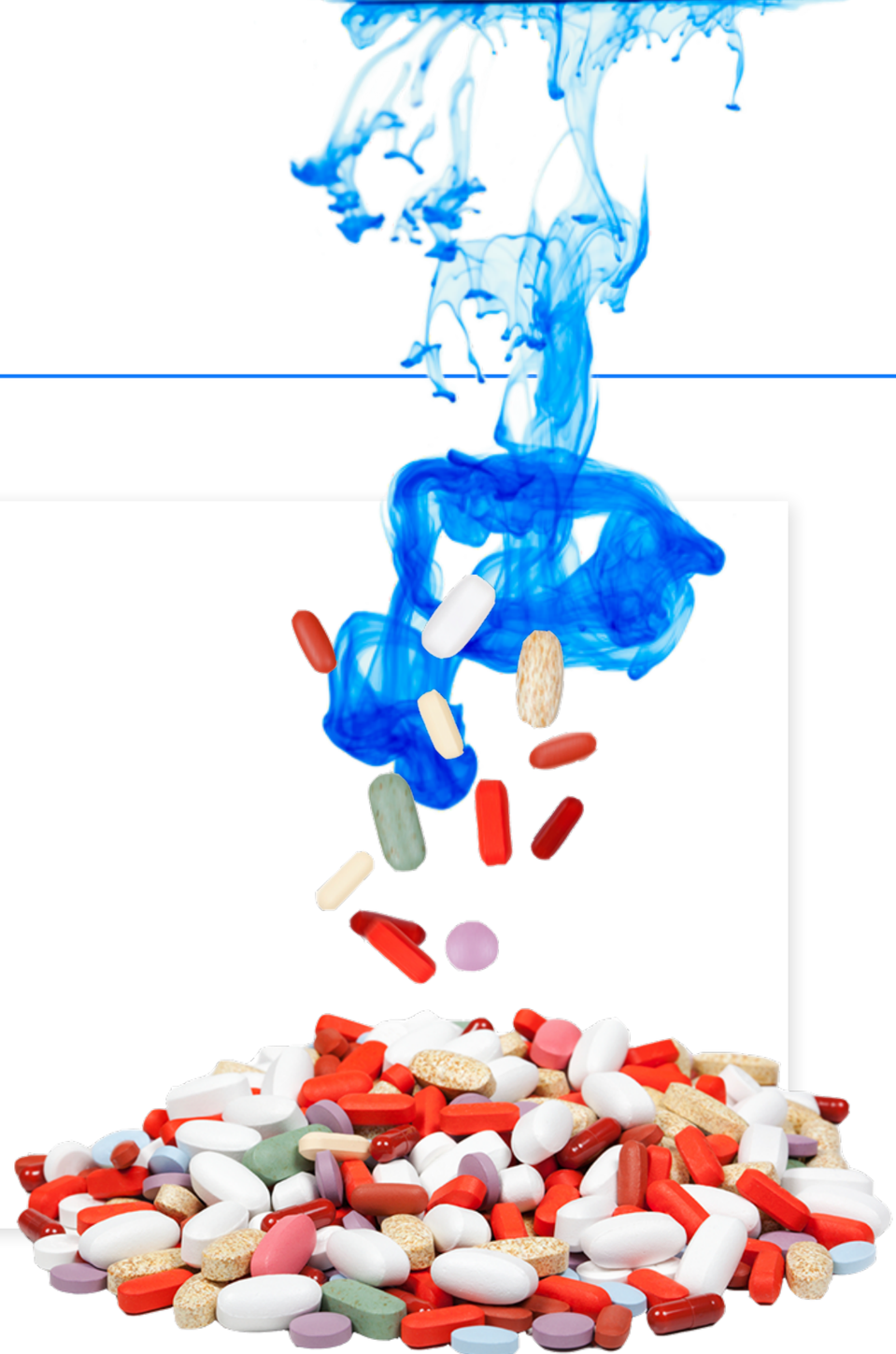
มหาวิทยาลัยขอนแก่น

ภญ.ภัทริยา จันทรทรัพย์

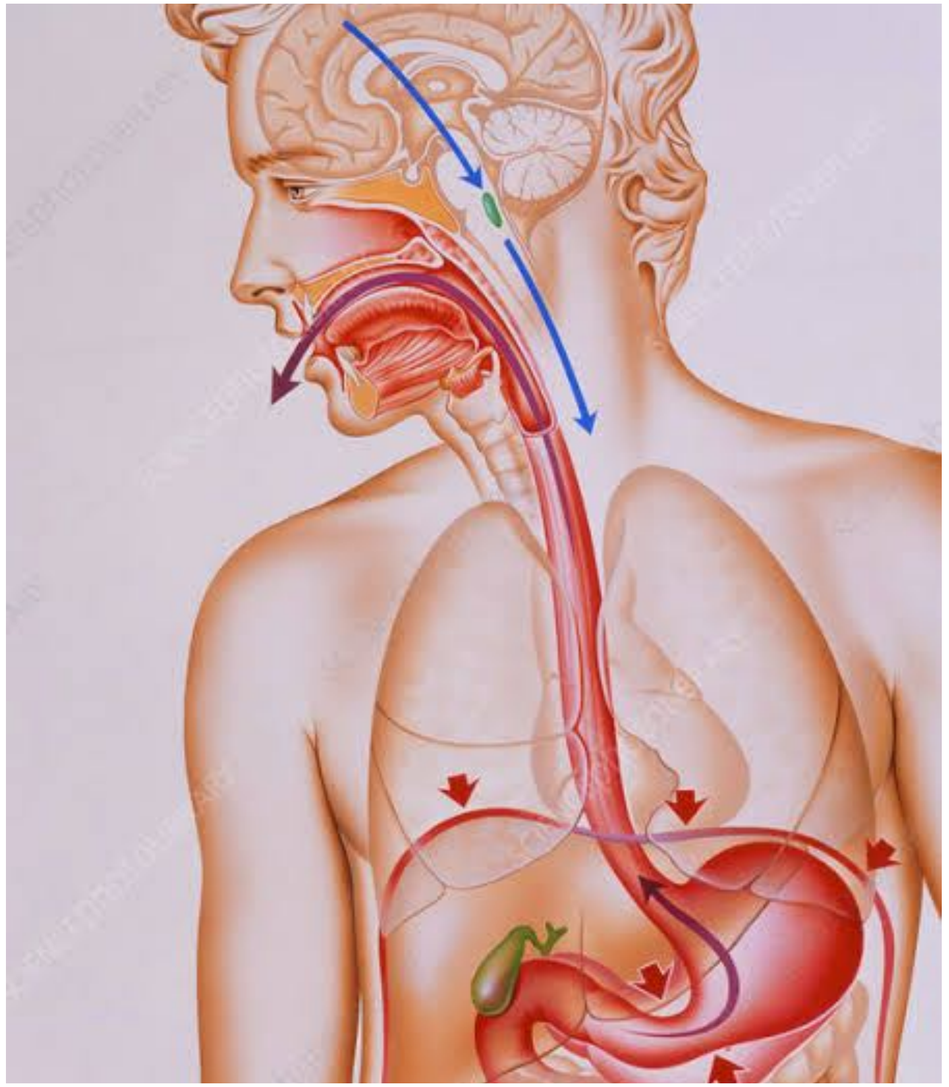
โรงพยาบาลกรุงเทพ

OBJECTIVE

- Assessing Emetogenic Risk
- Current Guidelines
- Recently Approved Agents
- Ongoing Controversies
- The Pharmacist's Role



Assessing Emetogenic Risk



Assessing Emetogenic Risk

- Should be completed for each patient
  - Before the start of anticancer therapy
  - Before any subsequent CMT cycles
- Prophylactic medications:
  - Scheduled throughout the period of risk
    - 4 days for a single-day HEC regimen
    - 3 days for MEC
- Breakthrough agent: different pharmacologic class

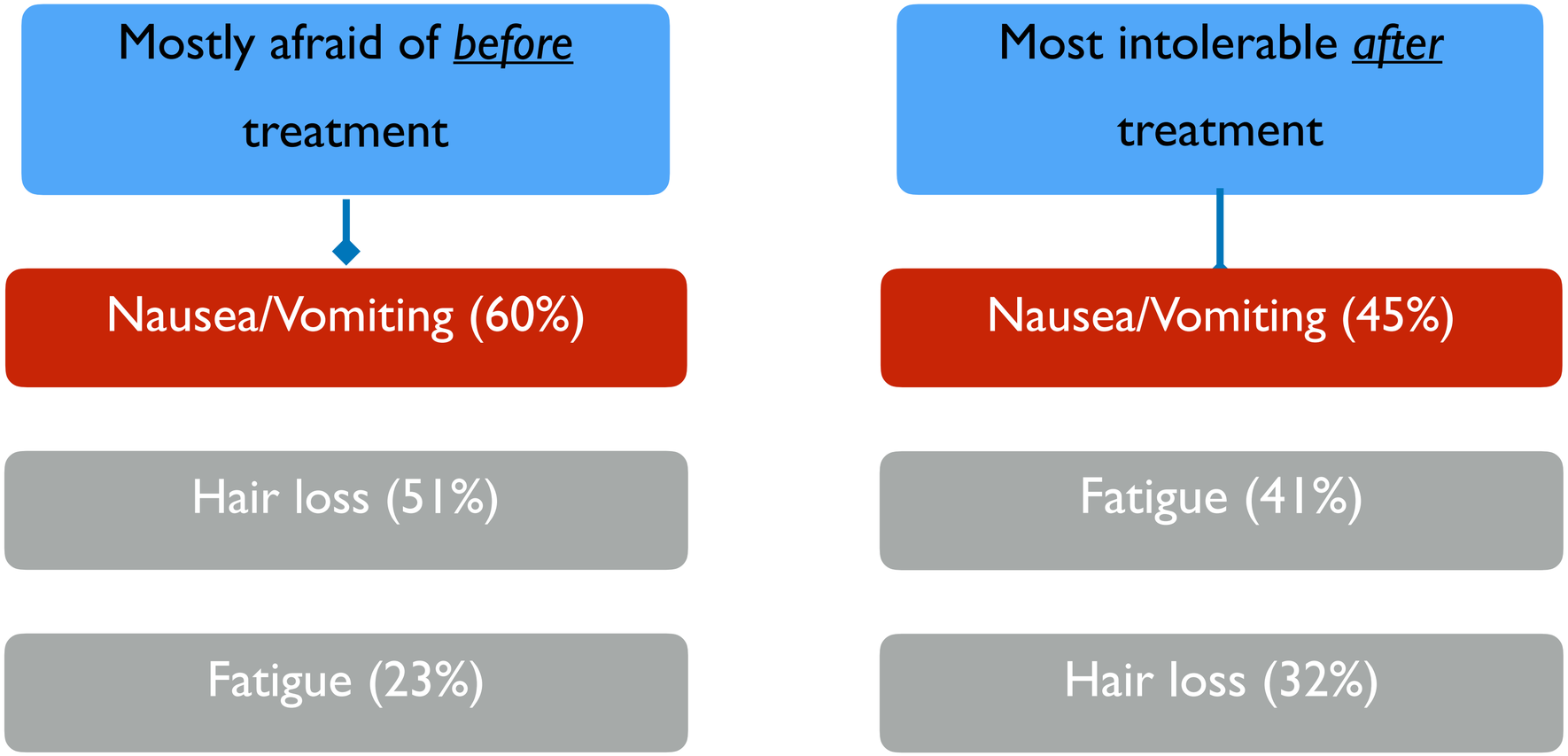
- "CINV is much easier to prevent than it is to treat,"

"It's really key to counsel our patients to make sure they understand how important it is to be compliant with their scheduled medications, and to use breakthrough the moment they start to feel nauseous."

Assessing Emetogenic Risk

- Determining emetogenic risk is fairly straightforward when administering single-agent CMT, but when a multi-agent regimen is used, it should be based on the drug in the regimen with the highest emetic risk.
- Ex:
  - Cisplatin (HEC) plus etoposide (LEC) would be **HEC**, whereas oxaliplatin (MEC) plus fluorouracil (5-FU) (LEC) plus leucovorin (MiniEC) would be **MEC**.
  - In the case of **2 MEC drugs** (ie, an anthracycline plus cyclophosphamide), the regimen should be considered **HEC**.

Patient Perception



Lorusso. D, et al. Cancer Care 2017, 26: e12618.

CONSEQUENCES

Increase Cost of treatment

Reduce treatment compliance

Impair Quality of life

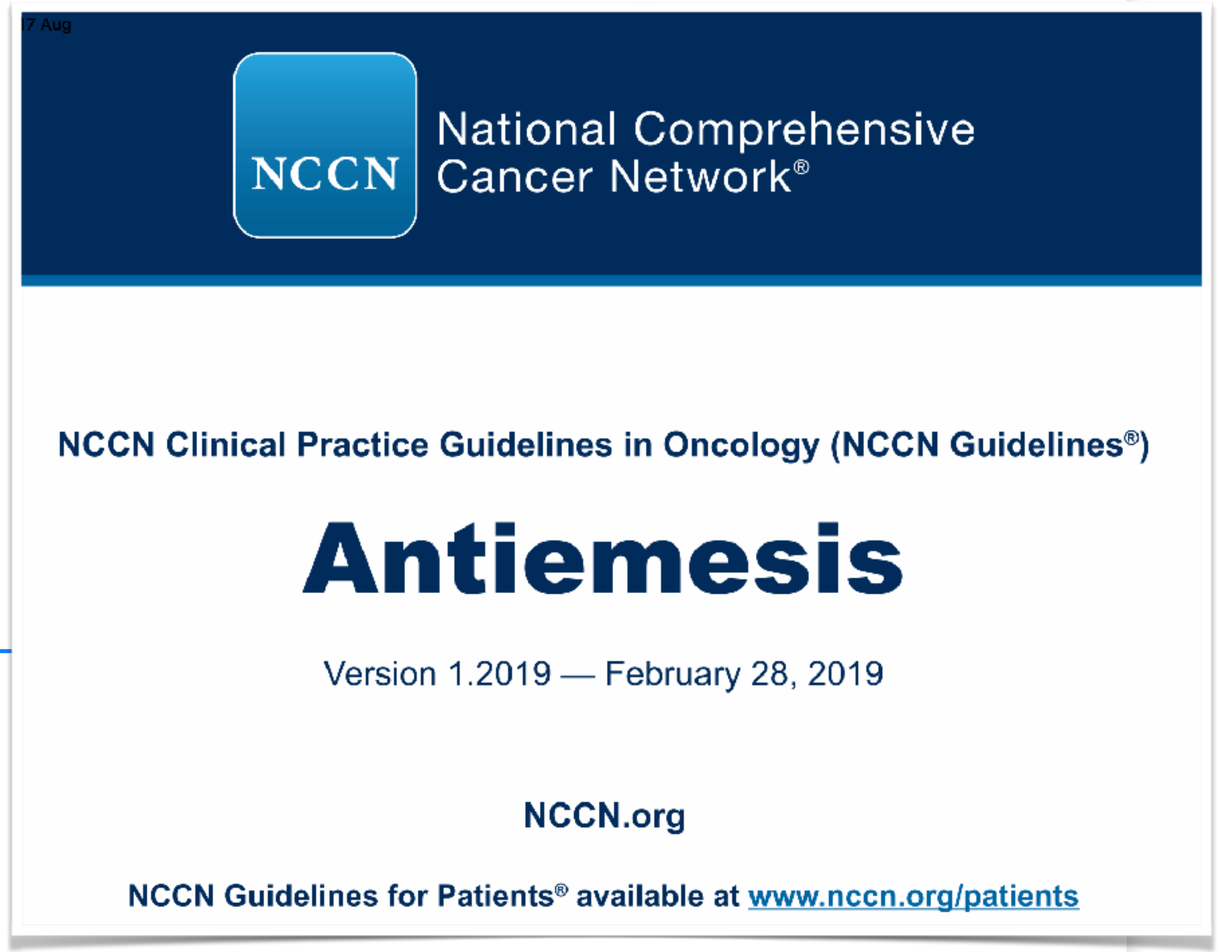
Compromised outcome

Ritter Jr HL et al. Cancer Invest 1998;16:87–93
Ballatori E, et al.Health Qual Life Outcomes. 2003; 1: 46.
Ihbe-Heffinger A, et al.Annals of Oncology 15: 526–536, 2004

Assessing Emetogenic Risk

- Nausea remains a more significant problem than vomiting.
  - Many physicians and nurses think CINV is fairly well controlled
  - But **patient perceptions** tend to be different
- **A 2015 HOPA survey** that assessed perceptions about CINV revealed numerous misconceptions, including the myth that nausea and vomiting indicate that the CMT is working, and the belief that CINV is simply to be expected.
  - Patients also commonly think that as long as they are not vomiting, their CINV is being controlled

Current Guideline



Emetogenic	Recommendation	
HEC	วันที่ 1 (Acute phase)	วันที่ 2,3,4 (Delayed phase)
	A: NK_1RAs* plus $5HT_3$RAs plus dex†	A: Aprepitant 80mg PO on days 2,3Ω plus dex on days 2,3,4‡
	B: OLN# plus palonosetron IV plus dex†	B: OLN# on days 2,3,4
	C: OLN# plus NK_1RAs* plus $5HT_3$RAs plus dex†	C: OLN# on days 2,3,4 plus Aprepitant 80mg PO on days 2,3Ω plus dex on days 2,3,4‡
MEC	วันที่ 1 (Acute phase)	วันที่ 2,3 (Delayed phase)
	D: $5HT_3$RAs plus dex†	D: dex on days 2,3‡ or $5HT_3$RAs on days 2,3¥
	E: OLN# plus palonosetron IV plus dex†	E: OLN# on days 2,3
	F: NK_1RAs* plus $5HT_3$RAs plus dex†	F: Aprepitant 80mg PO on days 2,3Ω +/- dex on days 2,3‡
LEC	ให้บริหารยาต่อไปนี้ (ตามความเหมาะสม) ก่อนให้ยาเคมีบำบัด (ในแต่ละวัน): Dex หรือ metoclopramide หรือ prochlorperazine หรือ $5HT_3$RAs	
miniEC	No routine prophylaxis	

Current Guideline

- Olanzapine improves outcomes when added to a NK_1RA plus a $5\text{-}HT_3RA$ plus DEX and is now considered a standard-of-care option for patients treated with cisplatin-based and other HEC regimens, (ASCO, NCCN)

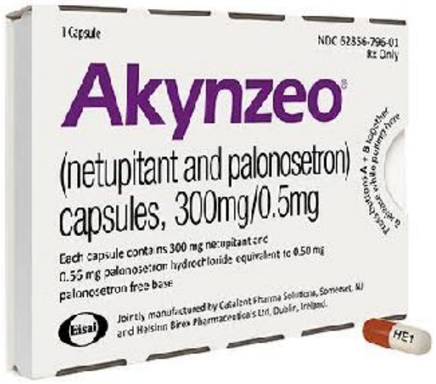
- These guidelines also recommend that an **NK_1RA** be added to a prophylactic regimen of a **$5\text{-}HT_3RA$ plus DEX** for patients receiving carboplatin-based CMT. Olanzapine with cisplatin-based and other HEC regimens, (ASCO, NCCN)

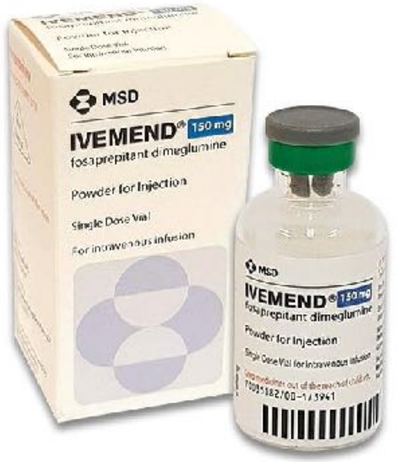
Current Guideline

- If a prophylactic antiemetic regimen does not contain an NK_1 RA, a single dose of granisetron extended release injection or IV palonosetron are the preferred 5-HT_3RAs, per NCCN guidelines

- "If olanzapine wasn't used on day one, consider it your breakthrough option"

Approved Agent in Thailand





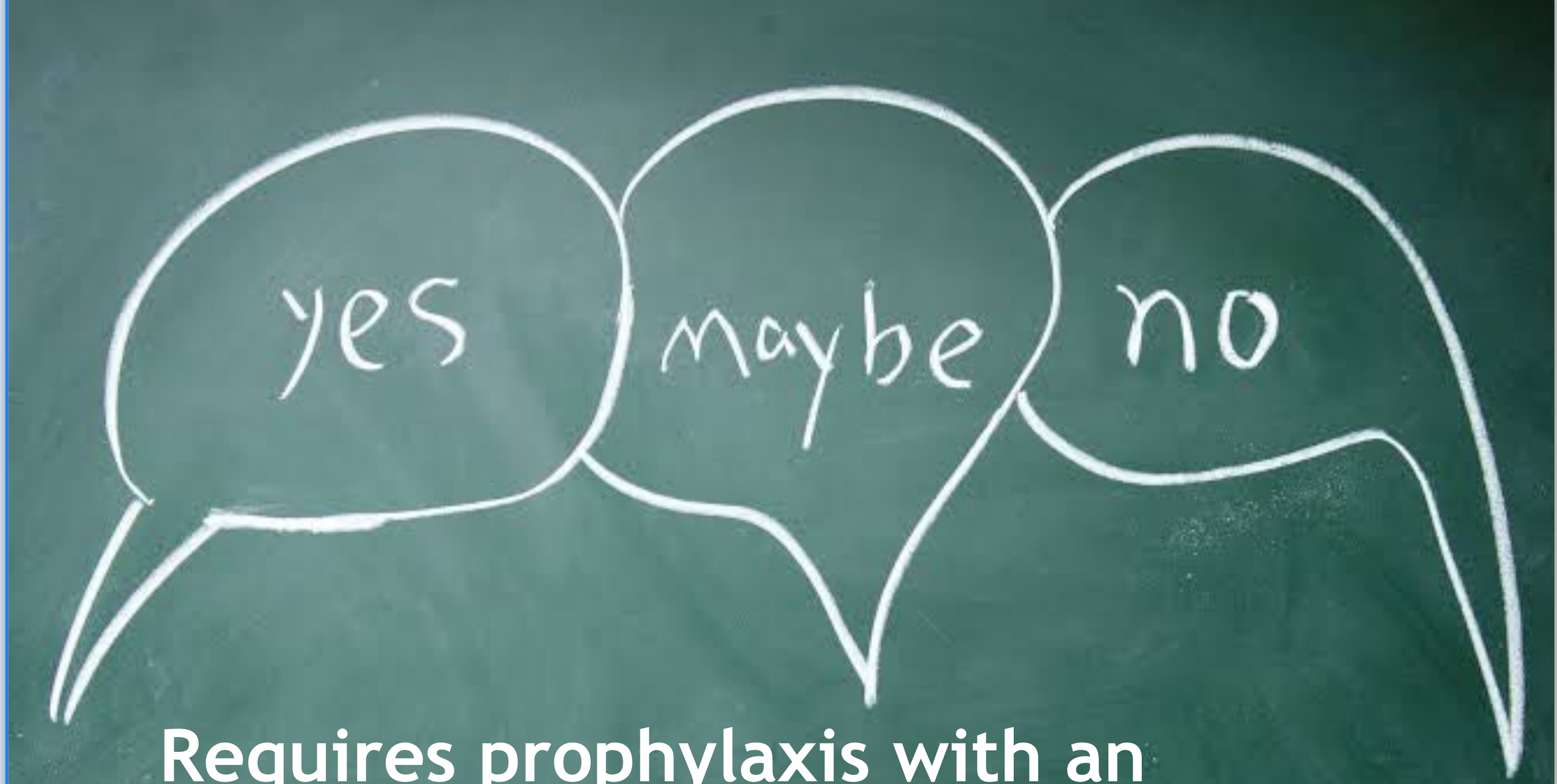
OLANZAPINE

- **Olanzapine: Available orally, including dispersive tablet**
- Phase II and phase III trials have indicated antiemetic activity
  - Methodologic issues have troubled most trials
- **ADRs:** sedation at a higher level than with other agents
- **Affects a variety of neurotransmitter receptors**
  - Different than most modern antiemetic
  - Implications: broader spectrum…but potential of more side-effects

New combination: NK_1RA+$5HT_3RA$

- **New combination**
  - **Oral** routenetupitant/palonosetron
- Both fixed-combination products
  - **Long-acting** NK_1RA + **Long-acting** 5-HT_3RA
  - **Single dose**
- **Indication:** prevention of acute and delayed CINV
- **ADR:** Headache, fatigue

Ongoing Controversies



Requires prophylaxis with an NK_1RA or olanzapine

NK_1RA or olanzapine

NK_1RA

-

Olanzapine

- A phase I trial of **olanzapine** (Zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group study.
  - OLN 10 mg
  - DLT: sedation
- Passik SD, et al. Cancer Invest, 2004:22(3):383-8.

NK_1RA or olanzapine

NK_1RA

A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC)

- NEPA administered only on day 1 was non-inferior to a 3-day oral APR/GRAN regimen in preventing CINV associated with HEC

Zhang L, et al, Ann Oncol. 2018;29(2):452-458

Olanzapine

- A Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial.
  - Short term use of olanzapine appears to be effective in controlling CINV in patients receiving HEC
  - $5HT_3RA$ gen2

Navari RM, et al, J Support Oncol, 2011:9(5):188-95.

NK_1RA or olanzapine

NK_1RA

- Very good in term of safety profile
- Most common ADR is mild fatigue, headache, constipation
  - Gralla RJ, et al. Ann Oncol. 2014 Jul;25(7):1333-9.

Olanzapine

- Olanzapine appears to have significant efficacy in delayed nausea
- Olanzapine vs DEX
  - Tan L, et al, J Exp Clin Cancer Res, 2009:23;28:131.
- Olanzapine vs Aprepitant
  - Navari RM, et al, J Support Oncol, 2011:9(5):188-95.

NK_1RA or olanzapine

NK_1RA

- Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial
  - Effective and safe in pediatric population
  - Kang HJ, etal. Lancet Oncol. 2015 Apr; 16(4):385-94.

Olanzapine

- The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy.
  - Olanzapine effective in "Breakthrough CINV" Olanzapine vs Metoclopramide
  - Navari RM, et al, Support Care Cancer, 2013:21(6):1655-63.

NK_1RA or olanzapine

NK_1RA

- Aprepitant also shown its safety in other setting include hematopoietic stem cell transplantation (both autologous and allogeneic)
  - Bubalo J, etal. Bone Marrow Transplant. 2018;53(8):1010-1018
  - Uchida M, et al.Pharmacotherapy. 2013; 33(9): 893–901.
  - Junagadhwalla M, et al. Blood 2005 106:5329;

Olanzapine

- Effectiveness of olanzapine for the treatment of breakthrough chemotherapy induced nausea and vomiting.
- Olanzapine effective in "Breakthrough CINV"
  Olanzapine single arm
- Chanthawong S, et al, J Med Assoc Thai 2014;97(3):349-55.

NK_1RA or olanzapine

NK_1RA

- Apprepitant also approved in post operative nausea vomiting (PONV)
  - Meta-analysis shows lower need for rescue antiemetic and a higher complete response when compare with 5-HT
  - Singh PM, et al. Postgrad Med J. 2016;92(1084):87-98

Olanzapine

- Olanzapine versus fosaprepitant for the prevention of concurrent chemotherapy radiotherapy-induced nausea and vomiting.
- Olanzapine effective in patients receiving CCRT
- Olanzapine vs Fosaprepitant
- Navari RM, et al, J Community Support Oncol, 2016:14(4):141-7.

The Oncologist®

Symptom Management and Supportive Care

Olanzapine-Based Triple Regimens Versus Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy: A Network Meta-Analysis

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Departments of [a]Medical Oncology and [b]Clinical Research, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, People's Republic of China

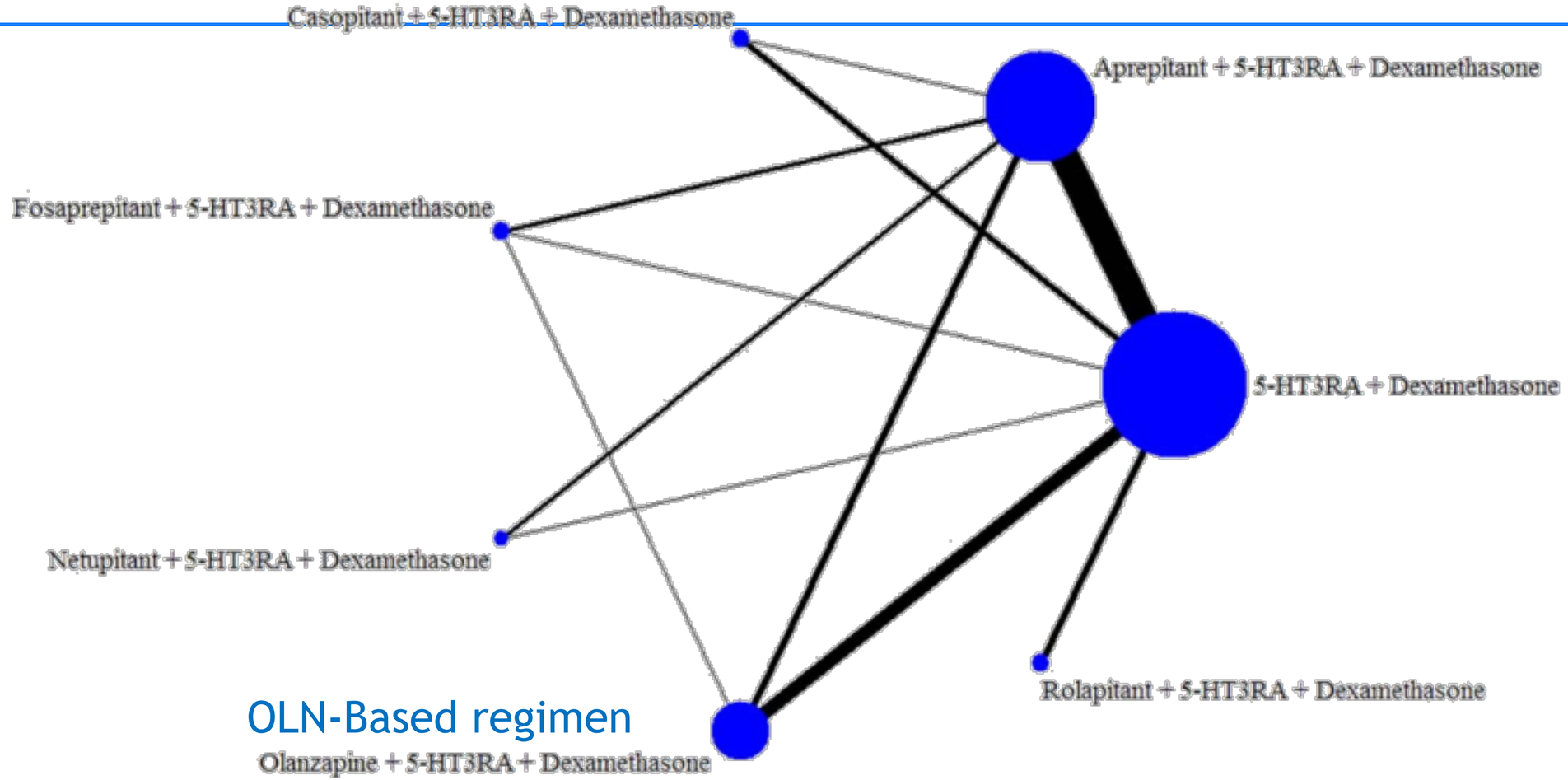
[†]Contributed equally

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Chemotherapy-induced nausea and vomiting • Highly emetogenic chemotherapy • Olanzapine • Neurokinin-1 receptor antagonists • Nausea • Network meta-analysis

Zhang Z, et al. The Oncologist 2018;23:603-616

Network established for multiple treatment comparisons of olanzapine-based triple regimens and different NK_1RAs-based triple regimens for patients with HEC



Zhang Z, et al. The Oncologist 2018;23:603–616

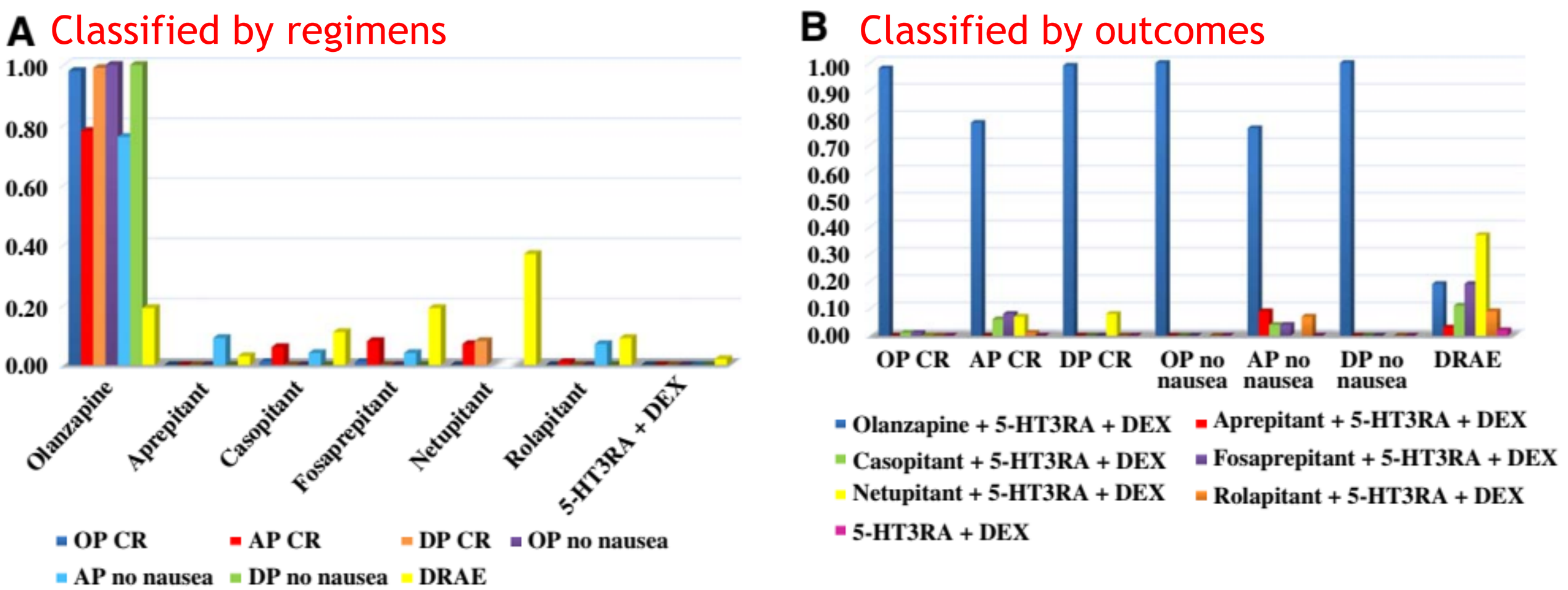
Binary comparison of olanzapine + 5-HT_3RA + DEX regimens versus NK_1-RA + 5-HT_3RA + DEX regimens for antiemetic efficacy

Outcome	No. of trials (no. of participants)	OR[a] (95% CI) in random model	Effect size		Heterogeneity	
			Z	p value	p value	I^2, %
Overall phase CR	5 (509)	1.16 (0.78–1.74)	0.73	.46	.96	0
Acute phase CR	5 (509)	2.13 (0.97–4.68)	1.87	.06	.20	34
Delayed phase CR	5 (513)	1.27 (0.84–1.92)	1.15	.25	.96	0
Overall phase no nausea	5 (509)	**2.45 (1.34-4.48)**	2.92	.004	.11	47
Acute phase no nausea	5 (509)	1.10 (0.68–1.80)	0.40	.69	.81	0
Delayed phase no nausea	5 (509)	**3.07 (2.09-4.52)**	5.71	<.001	.52	0

a Represents ORolanzapine-based triple/NK1-RA-based triple in cancer patients using olanzapine 1 5-HT3RA 1 DEX regimens or NK1-RA 1 5-HT3RA 1 DEX regimens in preventing chemotherapy-induced nausea and vomiting.

Abbreviations: 5-HT3RA, serotonin receptor antagonist; CI, confidence interval; CR, complete response; DEX, dexamethasone; I2, I-square results;NK1-RA, neurokinin-1 receptor antagonist; OR, odds ratio; Z, Z Test results.

Zhang Z, et al. The Oncologist 2018;23:603–616



Distribution of **probabilities of each CINV regimen** being ranked first place based on network, **classified by regimens (A)** and **by outcomes (B).A**

Abbreviations: 5-HT3RA, serotonin receptor antagonist; AP, acute phase; CR, complete response; DEX, dexamethasone; DP, delayed phase; DRAE, drug-related adverse event; OP, overall phase.

Zhang Z, et al. The Oncologist 2018;23:603–616

Supportive Care in Cancer
https://doi.org/10.1007/s00520-018-4400-1

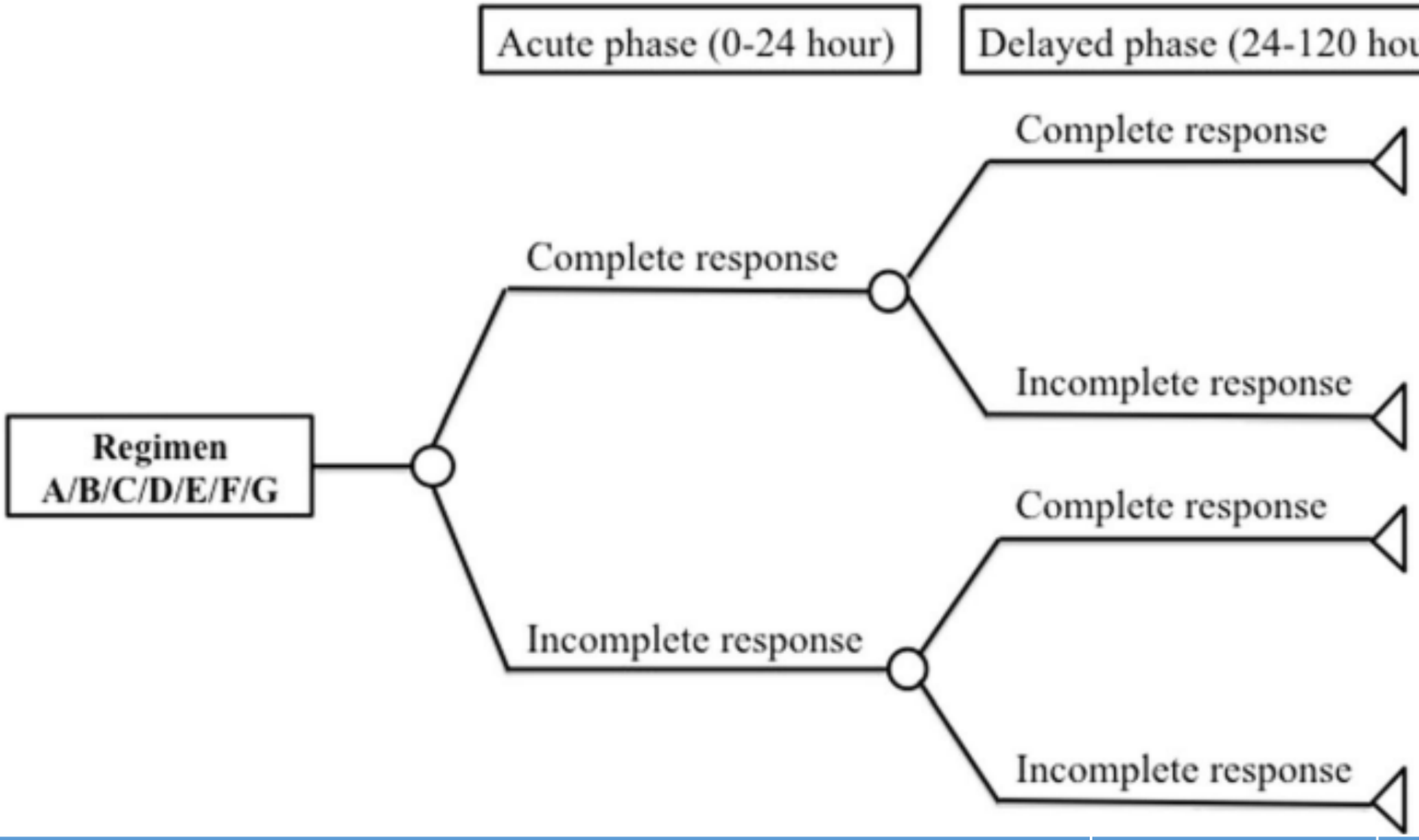
ORIGINAL ARTICLE

Cost-effectiveness analysis of olanzapine-containing antiemetic therapy for managing highly emetogenic chemotherapy in Southeast Asia: a multinational study

Suthan Chanthawong[1] · Yi Heng Lim[2] · Suphat Subongkot[1] · Alexandre Chan[3,4] · Rizka Andalusia[5] · Ros Suzanna Ahmad Bustamam[6] · Nathorn Chaiyakunapruk[2,7,8,9]

Received: 19 January 2018 / Accepted: 3 August 2018

Chanthawong S, et al. Support Care Cancer. 2019;27(3):1109-1119.



(A) DEX + 5HT3RA1, (Ref.)

(B) DEX + 5HT3RA2,

(C) DEX + 5HT3RA1 + OLN,

(D) DEX + 5HT3RA2 + OLN,

(E) DEX + 5HT3RA1 + APR,

(F) DEX + 5HT3RA2 + APR, and

Parameters	Thailand	Malaysia	Singapore	Indonesia	Ref
Complete response (CR) rate (A: DEX + 5HT3RA1)					
CR in acute phase	0.65	0.55	0.68	0.33	*
CR in delayed phase (following CR in acute phase)	0.36	0.51	0.71	0.37	
CR in delayed phase (following CINV in acute phase)	0.36	0.11	0.30	0.30	

Chanthawong S, et al. Support Care Cancer. 2019;27(3):1109-1119.

Risk ratio of CR and health state utility model estimates

Parameter	Base case	Range	Reference(s)
Risk ratio*			
Acute CINV			
A: DEX + 5HT3RA1	Reference		
B: DEX + 5HT3RA2 ★	1.538	1.310–1.806	NMA†
C: DEX + 5HT3RA1 + OLN	1.084	0.887–1.324	
D: DEX + 5HT3RA2 + OLN ★	2.370	1.342–4.186	
E: DEX + 5HT3RA1 + APR	1.671	0.662–4.217	
F: DEX + 5HT3RA2 + APR ★	1.621	1.123–2.342	
G: DEX + 5HT3RA2 + OLN + APR ★	3.313	1.925–5.701	
Delayed CINV			
A: DEX + 5HT3RA1	Reference		
B: DEX + 5HT3RA2 ★	1.577	1.440–1.727	NMA‡
C: DEX + 5HT3RA1 + OLN ★	1.227	1.109–1.358	
D: DEX + 5HT3RA2 + OLN ★★★	17.788	4.466–70.850	
E: DEX + 5HT3RA1 + APR ★	2.382	1.578–3.595	
F: DEX + 5HT3RA2 + APR ★	1.982	1.626–2.416	
G: DEX + 5HT3RA2 + OLN + APR ★	2.482	1.858–3.315	

Chanthawong S, et al. Support Care Cancer. 2019;27(3):1109-1119.

Implications for Practice

- According to the results of this study, **olanzapine-based triple antiemetic regimens** were **superior in both overall and delayed-phase nausea control** when compared with various neurokinin-1 receptor antagonists-based triple regimens in patients with HEC.
- Olanzapine-based triplet was **outstanding** in terms of **nausea control and drug price**.
- For cancer patients with HEC, especially those suffering from delayed-phase nausea, olanzapine-based triple regimens should be an optional antiemetic choice.

Zhang Z, et al. The Oncologist 2018;23:603–616

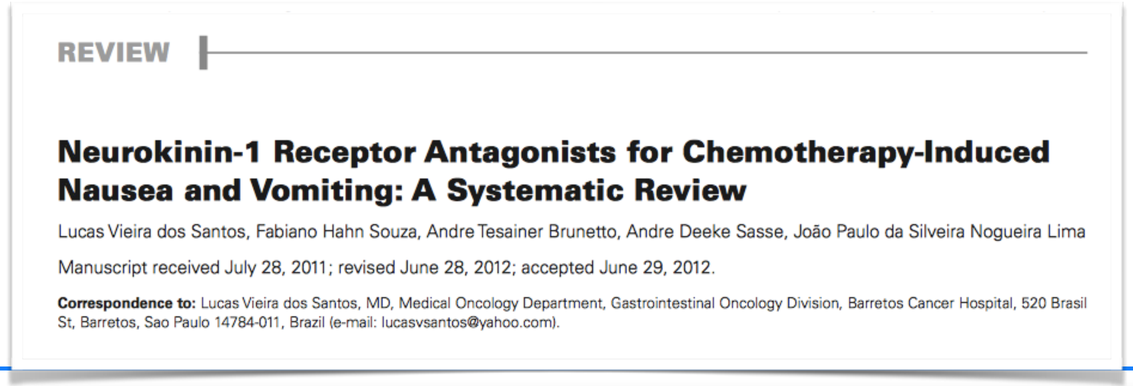
REVIEW

Neurokinin-1 Receptor Antagonists for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review

Lucas Vieira dos Santos, Fabiano Hahn Souza, Andre Tesainer Brunetto, Andre Deeke Sasse, João Paulo da Silveira Nogueira Lima

Manuscript received July 28, 2011; revised June 28, 2012; accepted June 29, 2012.

Correspondence to: Lucas Vieira dos Santos, MD, Medical Oncology Department, Gastrointestinal Oncology Division, Barretos Cancer Hospital, 520 Brasil St, Barretos, Sao Paulo 14784-011, Brazil (e-mail: lucasvsantos@yahoo.com).



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- Seventeen trials (8740 patients)

Endpiont	With NK-1 RA	Without NK-1 RA	OR and P value
CR (over all)	72%	54%	OR = 0.51, P < .001

- **Increase rate of complete response in the acute phase (OR 0.56, 95% CI 0.48 to 065; 15 trials; I^2=22%)**
- **In the delayed phase (OR 0.48, 95% CI 0.42 to 0.56; 15 trials; I^2=47%)**
- **Benefit in both HEC and MEC**

dos Santos LV, et al. J Natl Cancer Inst. 2012 Sep 5;104(17):1280-92.

Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-04824-y

ORIGINAL ARTICLE

Cost-effectiveness of a fixed combination of netupitant and palonosetron (NEPA) relative to aprepitant plus granisetron (APR + GRAN) for prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a trial-based analysis

Marc Botteman[1] · Katharina Nickel[2] · Shelby Corman[1] · Marco Turini[3] · Gary Binder[4]

Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-04824-y

ORIGINAL ARTICLE

Check for updates

Cost-effectiveness of a fixed combination of netupitant and palonosetron (NEPA) relative to aprepitant plus granisetron (APR + GRAN) for prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a trial-based analysis

Marc Botteman[1] · Katharina Nickel[2] · Shelby Corman[1] · Marco Turini[3] · Gary Binder[4]

- Data from a phase 3 trial show highly cost-effective of NEPA in post-HEC CINV prevention.
- Significant total per-patient cost reduction of $309 ($943 vs $1252; 95% CI $4–$626)
  - $258 in lower medical costs of CINV-related event
  - $45 in lower study drug costs
  - Actual savings may be higher, e.g. impact of CINV-related chemotherapy discontinuation

Implications for Practice

- NK-1 RA based regimen is outstanding in term of efficacy and safety profile
- Most frequent ADR is mild and not interfere with patient daily activity
- Novel agents are convenient for patient: single dose
- Aprepitant is approved in more indications and in special population esp. pediatric

Zhang Z, et al. The Oncologist 2018;23:603–616

Controversy

- Controversy continues over the optimal dose of DEX, but the dose can be individualized based on patient-specific factors, concurrent medications, ADRs, and CMT regimen
- More controversy surrounds carboplatin's emetogenicity.
- Carboplatin AUC of ≥4 is currently considered HEC (NCCN), or a unique category of MEC (ASCO)
- Lack of data for novel NK1-RA agent in some specific indication/ population

Zhang Z, et al. The Oncologist 2018;23:603–616

Controversy

- The preferred 5-HT3RA when no NK1RA is used is granisetron ER injection or palonosetron.
- When an NK1RA is used, there is no preferred 5-HT3RA agent, yet.

- "ASCO revised their guidelines in 2017 before granisetron ER [was approved], so this could change in the future,". As of now, there is also no preferred NK1 RA agent.

Hesketh PJ, et al. J Oncol Pract. 2017;13:825-830.

NCCN Guidelines: Antiemesis. Version 1.2019. www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.

Controversy

- In terms of HEC regimens, olanzapine has been established as non-inferior to an NK_1 RA regimen, and an NK_1 RA regimen added to olanzapine is better than an NK_1 RA regimen alone.
  - **Quadruplet vs. Triplet regimen**

- **To Be Continue .... Next Topic**

Zhang Z, et al. The Oncologist 2018;23:603–616

Pharmacist Roles

- Guard against over- or underutilization of antiemetics
- Antiemetic selection
- Drug–drug interactions
- Clinical trial results
- Practice guidelines
- Cost