



Supportive Care

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October 8, 2025

UW Medicine

What is supportive care?

- Encompasses significant amount of what an oncologist does – widely applicable
- Not specific to any oncologic disease
- Aimed at improving symptoms and tolerance of therapy
- Multiple topics
- Guidelines by NCCN, MASCC, ASCO, and others
- Palliative(Supportive Care), Survivorship, and Communication = 11% boards

Topics – covered today

Antiemesis

Anemia

Myeloid growth factors

Skeletal

Fatigue

Brief reviews – neuropathy, cachexia

Not covered: pain, mucositis, GI, distress, palliative care, infections, survivorship, chemotherapy dosing, IV access, immunotherapy toxicity management, VTE, smoking cessation, communication ...

Antiemesis

CINV Introduction

- N/V are the most common and feared symptoms of cancer chemotherapy
- Management of these symptoms is the most important determinant of the patient experience
- Innovation in this area has undoubtedly improved QOL and likely survival though improved adherence

Potential problems due to N/V:

- Metabolic disturbances
- Dehydration
- Anorexia
- Decline in PS
- Wound complications, esophageal tears
- Withdrawal from treatment

Definitions

- Acute onset N/V usually occurs within minutes to hours after chemotherapy administration and , it peaks after ~ 6 hours and commonly resolves within 24 hours

Delayed CINV

- Delayed = (>24hrs)
- Common with platins, cyclophosphamide, doxorubicin
- Cisplatin – peaks at 48-72 hours, can last up to a week
- The risk of N/V extends to at least 4 days after drug is given for agents of moderate to high emetogenic potential and patients should be protected through this period

Anticipatory CINV

- N/V before next chemotherapy
- a conditioned response
- estimates range from 20-60%
- main indication for benzodiazepines (lorazepam) in CINV

Refractory/Breakthrough CINV

- Breakthrough emesis occurs despite prophylactic treatment and/or requires “rescue” antiemetics
- Refractory emesis may occur during subsequent cycles following ineffective treatment in earlier cycles

CINV Risk Factors

Acute

Patient-related factors

- Age
- Gender
- Alcohol use
- previous CINV
- History of anxiety
- Prone to motion sickness
- Morning sickness during pregnancy

Chemotherapy-related factors

- Emetogenicity
- Combination regimens, dose
- Number of cycles
- Unfractionated regimens
- Infusion time

Delayed

Any predictive factor for acute CINV

Poor control of acute CINV

Concomitant drugs after chemotherapy
(i.e. opioids, antibiotics)

Low QOL score

Emetogenicity of Chemotherapy

- No universal classification system, NCCN guidelines
- High (> 90%) of patients experience emesis
- Moderate (30-90%)
- Low (10-30%)
- Minimal (< 10%)



EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS

LEVEL	AGENT
High emetic risk (>90% frequency of emesis) ^a	<ul style="list-style-type: none"> • AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1500 mg/m² • Dacarbazine • Datopotamab deruxtecan-dlnk • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Fam-trastuzumab deruxtecan-nxki • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin • Zolbetuximab-clzb^b
Moderate emetic risk (>30%–90% frequency of emesis) ^a	<ul style="list-style-type: none"> • Aldesleukin >12–15 million IU/m² or 600,000 IU/kg^c • Amifostine >300 mg/m² • Bendamustine • Busulfan • Carboplatin^b AUC <4 • Carmustine^b ≤250 mg/m² • Clofarabine • Cyclophosphamide^b ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin^d • Daunorubicin^d • Dinutuximab • Doxorubicin^d <60 mg/m² • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Epirubicin^d ≤90 mg/m² • Idarubicin^d • Ifosfamide^d <2 g/m² per dose • Irinotecan^d • Irinotecan (liposomal) • Lurbinectedin • Melphalan <140 mg/m² • Methotrexate^c ≥250 mg/m² • Mirvetuximab soravtansine-gynx • Naxitamab-gqqk • Oxaliplatin^d • Romidepsin • Temozolomide • Trabectedin^d

Table framework is based on the emetogenicity classifications described in the following publications: Hesketh PJ, et al. J Clin Oncol 1997;15:103-109; Grunberg SM, et al. Support Care Cancer 2011;19:S43-S47.

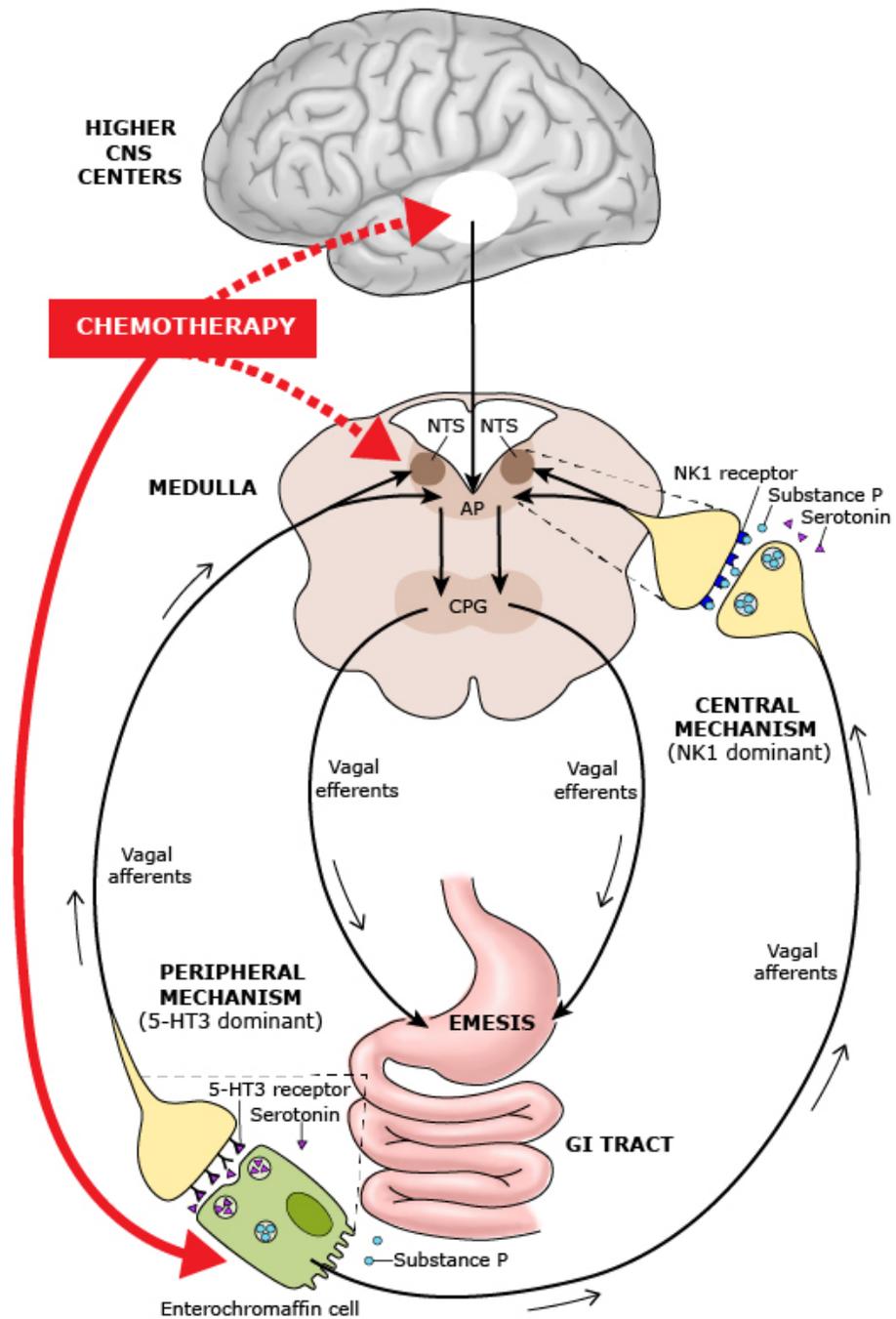


EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS

LEVEL	AGENT			
Low emetic risk (10%–30% frequency of emesis) ^{a,e}	<ul style="list-style-type: none"> • Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Amivantamab-vmjw • Arsenic trioxide • Axicabtagene ciloleucel^f • Azacitidine • Belinostat • Brentuximab vedotin • Brexucabtagene autoleucel^f • Cabazitaxel • Carfilzomib • Ciltacabtagene autoleucel^f • Copanlisib 	<ul style="list-style-type: none"> • Cytarabine (low dose) 100 mg/m² – 200 mg/m² • Docetaxel • Doxorubicin (liposomal) • Elranatamab-bcmm • Enfortumab vedotin-ejfv • Epcoritamab-bysp • Eribulin • Etoposide • Floxuridine • 5-Fluorouracil (5-FU) • Gemcitabine • Gemtuzumab ozogamicin • Idecabtagene vicleucel^f • Inotuzumab ozogamicin 	<ul style="list-style-type: none"> • Isatuximab-irfc • Ixabepilone • Lifileucel^f • Lisocabtagene maraleucel^f • Loncastuximab tesirine-lpyl • Methotrexate >50 mg/m² – <250 mg/m² • Mitomycin • Mitomycin pyelocalyceal solution • Mitoxantrone • Mogamulizumab-kpkc • Mosunetuzumab-axgb • Necitumumab • Omacetaxine 	<ul style="list-style-type: none"> • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Polatuzumab vedotin-piig • Pralatrexate • Tafasitamab-cxix • Tagraxofusp-erzs • Talimogene laherparepvec • Tebentafusp-tebn • Thiotepa • Tisagenlecleucel^f • Tisotumab vedotin-tftv • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis) ^{a,e}	<ul style="list-style-type: none"> • Alemtuzumab • Asparaginase^g • Atezolizumab • Atezolizumab and hyaluronidase-tqjs • Avelumab • Betibeglogene autotemcel^f • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cemiplimab-rwlc • Cetuximab • Cladribine • Cytarabine <100 mg/m² • Daratumumab • Daratumumab and hyaluronidase-fihj • Decitabine 	<ul style="list-style-type: none"> • Degarelix • Dexrazoxane • Dostarlimab-gxly • Durvalumab • Elotuzumab • Fludarabine • Fulvestrant • Glofitamab-gxbm • Goserelin • Histrelin • Imetelstat • Ipilimumab • Lanreotide • Leuprolide • Lovotibeglogene autotemcel^f • Luspatercept-aamt • Margetuximab-cmkb • Methotrexate ≤50 mg/m² • Nelarabine 	<ul style="list-style-type: none"> • Nivolumab • Nivolumab and hyaluronidase-nvhy • Nivolumab/relatlimab-rmbw • Obinutuzumab • Octreotide • Ofatumumab • Panitumumab • Pembrolizumab • Pertuzumab • Pertuzumab/trastuzumab and hyaluronidase-zzxf • Ramucirumab • Retifanlimab-dlwr • Rituximab • Rituximab and hyaluronidase • Siltuximab • Sirolimus-albumin 	<ul style="list-style-type: none"> • Talquetamab-tgvs • Tarlatamab-dlle • Teclistamab-cqyv • Temsirolimus • Tislelizumab-jsgr • Toripalimab-tpzi • Trastuzumab • Trastuzumab and hyaluronidase-oysk • Tremelimumab-actl • Triptorelin • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS

LEVEL	AGENT			
Moderate to high emetic risk ^a (≥30% frequency of emesis): Prophylaxis required on days of PO anticancer agent administration	<ul style="list-style-type: none"> • Azacitidine^y • Busulfan ≥4 mg/day • Ceritinib • Cyclophosphamide ≥100 mg/m²/day 	<ul style="list-style-type: none"> • Fedratinib • Lomustine (single day) • Midostaurin • Mitotane 	<ul style="list-style-type: none"> • Selinexor^z • Temozolomide >75 mg/m²/day • Temozolomide ≤75 mg/m²/day with concurrent RT 	
Moderate to high emetic risk ^{a,aa} (≥30% frequency of emesis): As needed (PRN) dosing is initially appropriate on days of PO anticancer agent administration	<ul style="list-style-type: none"> • Abemaciclib • Adagrasib • Avapritinib • Binimetinib • Bosutinib >400 mg/day • Cabozantinib • Crizotinib 	<ul style="list-style-type: none"> • Dabrafenib • Elacestrant • Enasidenib • Encorafenib • Estramustine • Etoposide 	<ul style="list-style-type: none"> • Imatinib >400 mg/day • Lenvatinib >12 mg/day • Niraparib • Olaparib • Procarbazine 	<ul style="list-style-type: none"> • Rucaparib • Tovorafenib • Trifluridine/tipiracil
Minimal to low emetic risk ^a (<30% frequency of emesis)	<ul style="list-style-type: none"> • Abiraterone • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Anastrozole • Apalutamide • Asciminib • Axitinib • Belzutifan • Bexarotene • Bicalutamide • Bosutinib ≤400 mg/day • Brigatinib • Busulfan <4 mg/day • Capecitabine • Capivasertib • Capmatinib • Chlorambucil • Cobimetinib • Cyclophosphamide <100 mg/m²/day • Dacomitinib • Darolutamide • Dasatinib • Decitabine and cedazuridine • Duvelisib 	<ul style="list-style-type: none"> • Eflornithine • Entrectinib • Enzalutamide • Erdafitinib • Erlotinib • Everolimus • Exemestane • Fludarabine • Flutamide • Fruquintinib • Futibatinib • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib ≤400 mg/day • Ivosidenib • Ixazomib • Lapatinib • Larotrectinib • Lenalidomide • Lenvatinib ≤12 mg/day • Letrozole • Lorlatinib • Megestrol 	<ul style="list-style-type: none"> • Melphalan • Mercaptopurine • Methotrexate • Momelotinib • Neratinib • Nilotinib • Nilutamide • Nirogacestat • Olutasidenib • Osimertinib • Pacritinib • Palbociclib • Pazopanib • Pemigatinib • Pexidartinib • Pirtobrutinib • Pomalidomide • Ponatinib • Pralsetinib • Quizartinib • Regorafenib • Relugolix • Repotrectinib • Ribociclib • Ripretinib • Ruxolitinib 	<ul style="list-style-type: none"> • Selpercatinib • Sonidegib • Sorafenib • Sotorasib • Sunitinib • Talazoparib tosylate • Tamoxifen • Tazemetostat • Temozolomide ≤75 mg/m²/day • Tepotinib • Thalidomide • Thioguanine • Tivozanib • Topotecan • Toremfifene • Trametinib • Tretinoin • Tucatinib • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat • Zanubrutinib



Biology of CINV

NTS: nucleus tractus solitarius
 AP: area postrema
 CPG: central pattern generator

From: UpToDate

Pharmacologic options for CINV

- 5HT₃ antagonists (ondansetron, dolasetron, granisetron, palonosetron)
- Corticosteroid (dexamethasone)
- Benzodiazepines (lorazepam)
- Phenothiazines** (prochlorperazine, promethazine)
- Butyrophenones** (droperidol, haloperidol)
- Olanzapine
- Cannabinoids (dronabinol)**
- Substituted benzamides (metoclopramide)**
- Antihistamine/Anticholinergics (diphenhydramine, scopolamine)**
- Substance P/NK₁ receptor antagonist (aprepitant, netupitant)

** low therapeutic index agents not discussed in this lecture

- No final common pathway has been discovered
- Current agents act on different receptor families
(M1, D2, H1, 5-HT3, NK1)
- No single agent expected to provide complete protection

Serotonin (5HT₃) in CINV

- Closely associated with acute phase CINV
- Chemotherapy administration causes release of serotonin from the GI tract, thereby stimulating emesis via vagus and greater splanchnic nerves, as well as the area postrema of the brain
- In early trials, 5HT₃ release was not found in delayed phase of CINV
- Palonosetron has efficacy for prevention of delayed emesis, but role of other 5HT₃ is debated

5-HT₃ receptor antagonists

- ondansetron (1991), granisetron, dolasetron, palonosetron (2003)
- Numerous studies have demonstrated the 5-HT₃ agents have same SE profile and efficacy*
- SE are mild – HA, constipation – counsel patients
- Steroids improve efficacy
- QTc prolongation (except palonosetron and ER formulations)
- Limited role in treatment of delayed phase N/V

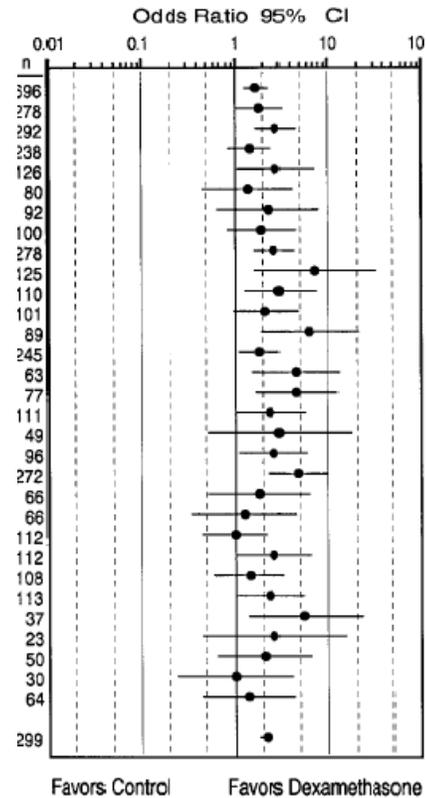
Palonsetron

- pharmacologically distinct
- 100-fold higher binding affinity for 5-HT₃R
- T_{1/2} ~ 40 hours
- As effective as traditional 5-HT₃ agents for acute CINV (single dose)
- Superior in preventing delayed emesis (single dose)

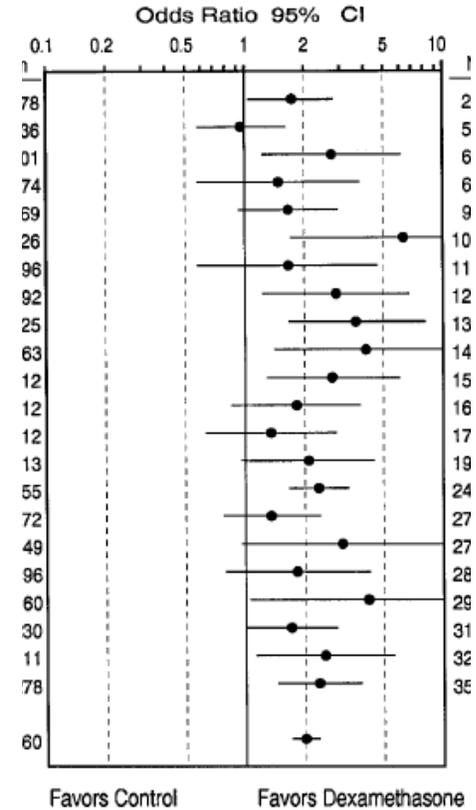
Dexamethasone addition to 5HT3

Meta-analysis of 32 studies showing OR of 2 vs 5HT3 monotherapy for acute and delayed phase

Acute Phase



Delayed Phase



(side note – dexamethasone induced hiccup -> prednisone)

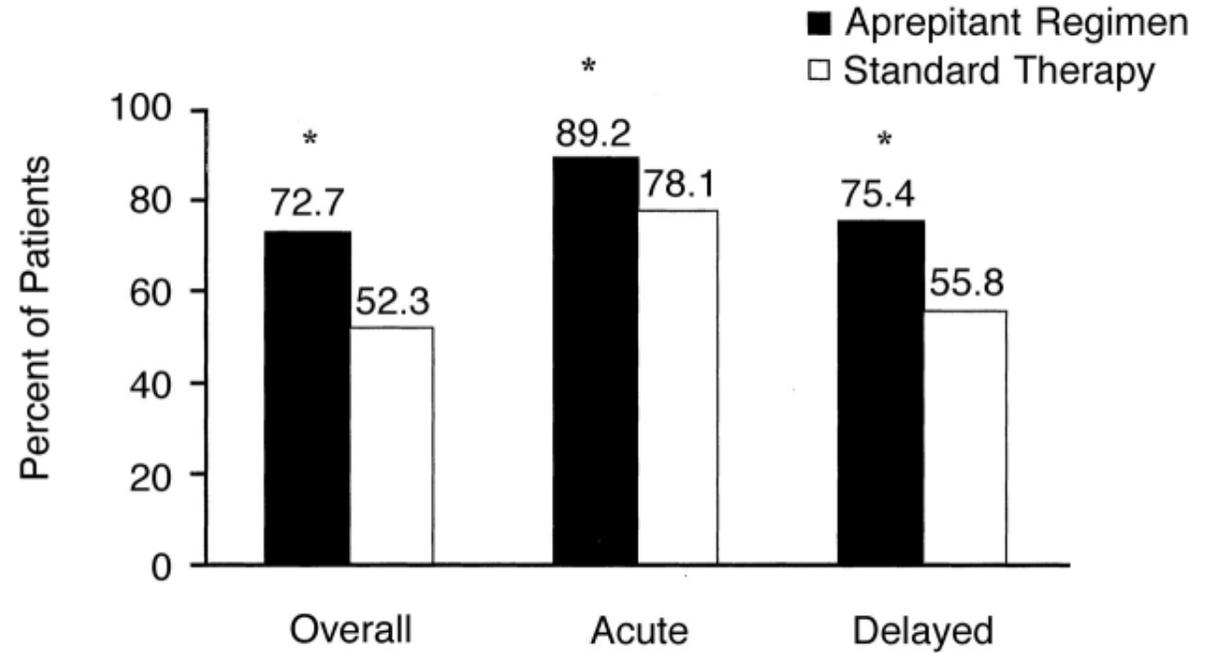
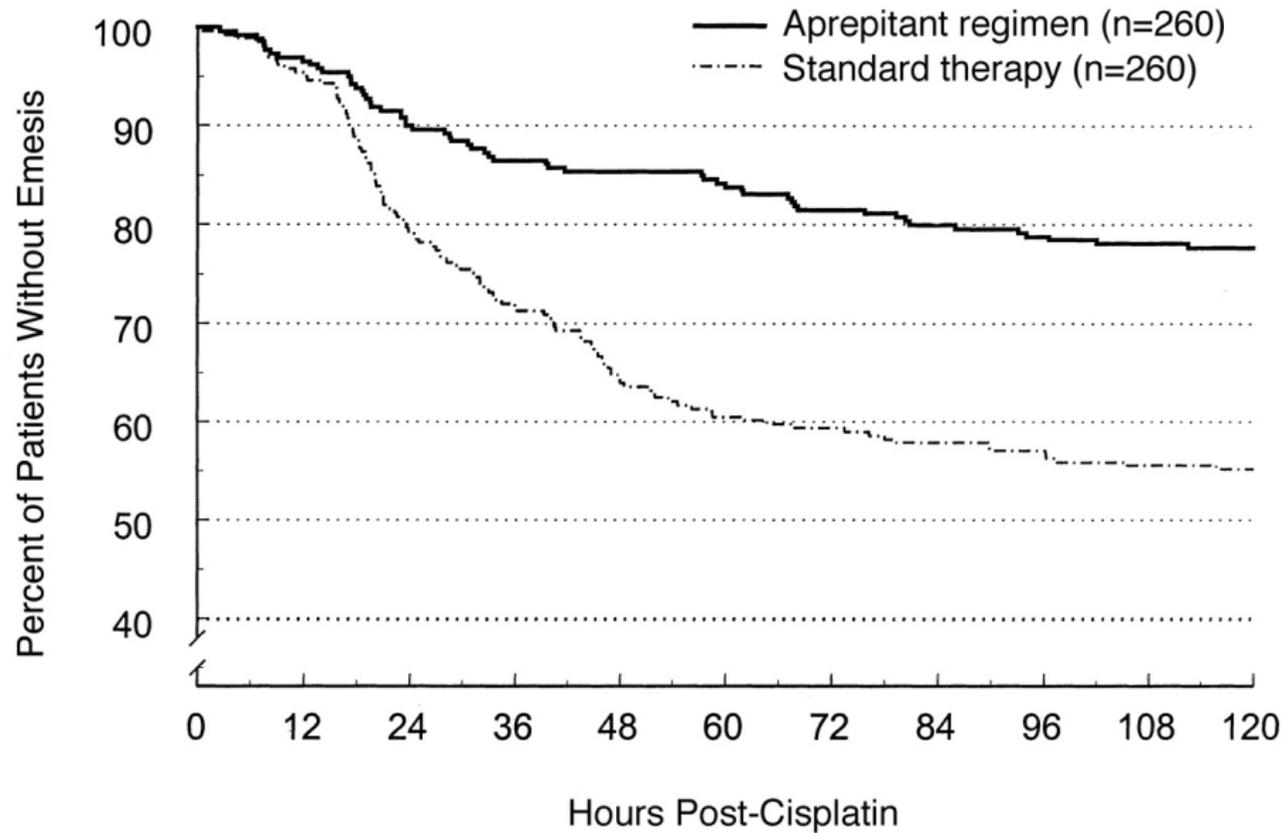
Ioannidis et al. JCO. PMID 11013282

Substance P / Neurokinin Receptors

Aprepitant/fosaprepitant, others

- Substance P: a member of the tachykinin family of neuropeptides
- Biological activity mediated by neurokinin (NK-1) receptor
- Substance P and NK-1 receptors located in brain stem dorsal vagal complex – nucleus tractus solitarius (NTS) and area postrema and the GI tract
- Beneficial in delayed > acute CINV, but use is in prevention
- Fosaprepitant 150 mg IV over ~30 min (polysorbate 80, HSR)
- Aprepitant 130mg IV over ~2 min
- Many drug interactions, ~CYP3A4 -reduce dexamethasone 50%

Kaplan-Meier curves demonstrating percentages of patients without emesis during the 120-hour study period.



Standard therapy – ondansetron d1, dexamethasone d1-4

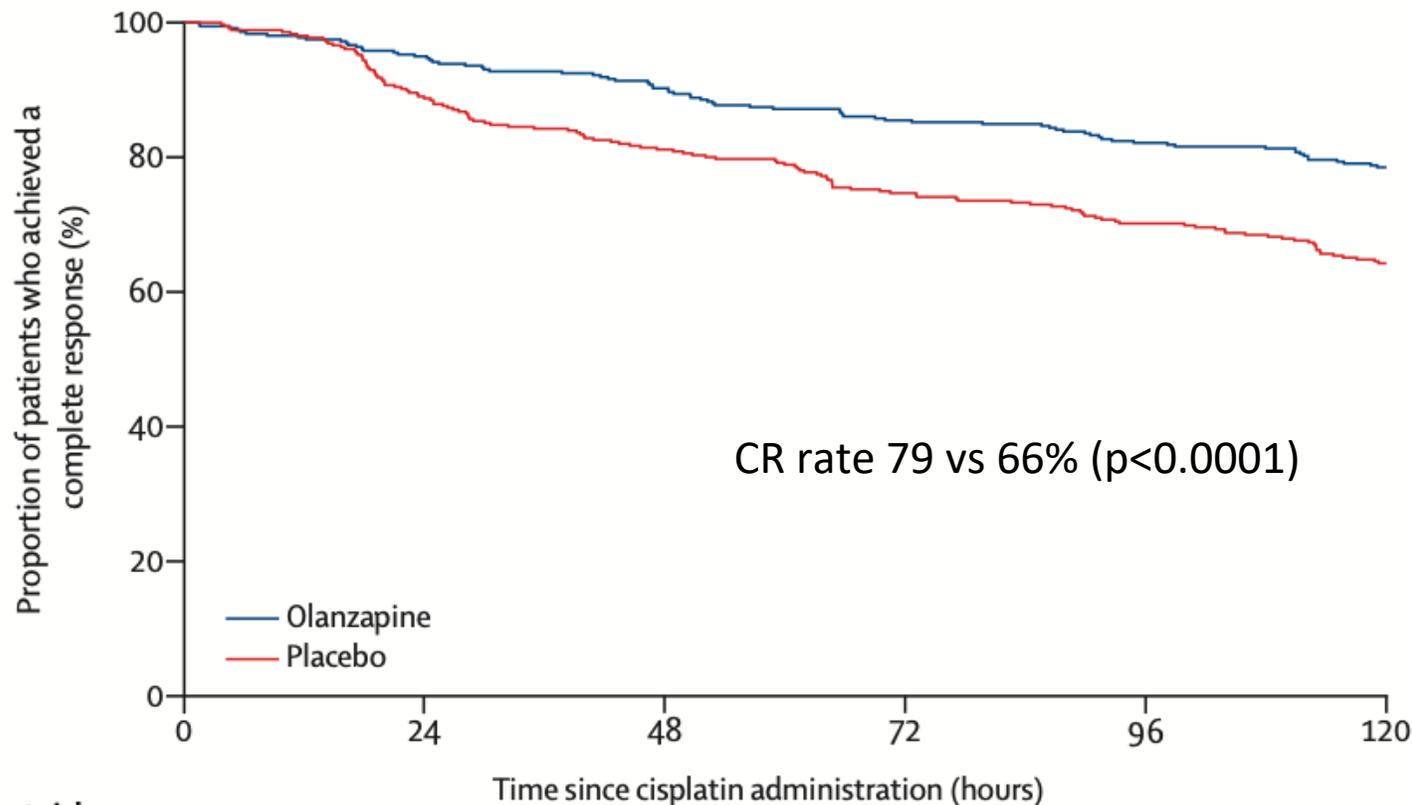
RCT: (olanzapine 10 mg vs placebo) + fosaprepitant, 5HT3, Dex

	CR Rate=no emesis or rescue(%)		No nausea (%) = primary endpt	
	Olanz	PCO	Olanz	PCO
0-24 hr	86	65	74	55
0-120 hr	64	40	37	22

All P < 0.01, N= 380

Side Effects: mild increase in **sedation** at day 2 (2/10 vs. 1/10) and increased appetite

Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE):



Number at risk

	0	24	48	72	96	120
Olanzapine	354	333	316	301	288	277
Placebo	351	308	282	259	244	224

cisplatin (≥ 50 mg/m²)
age 20 - 75 years,
ECOG 0–2.

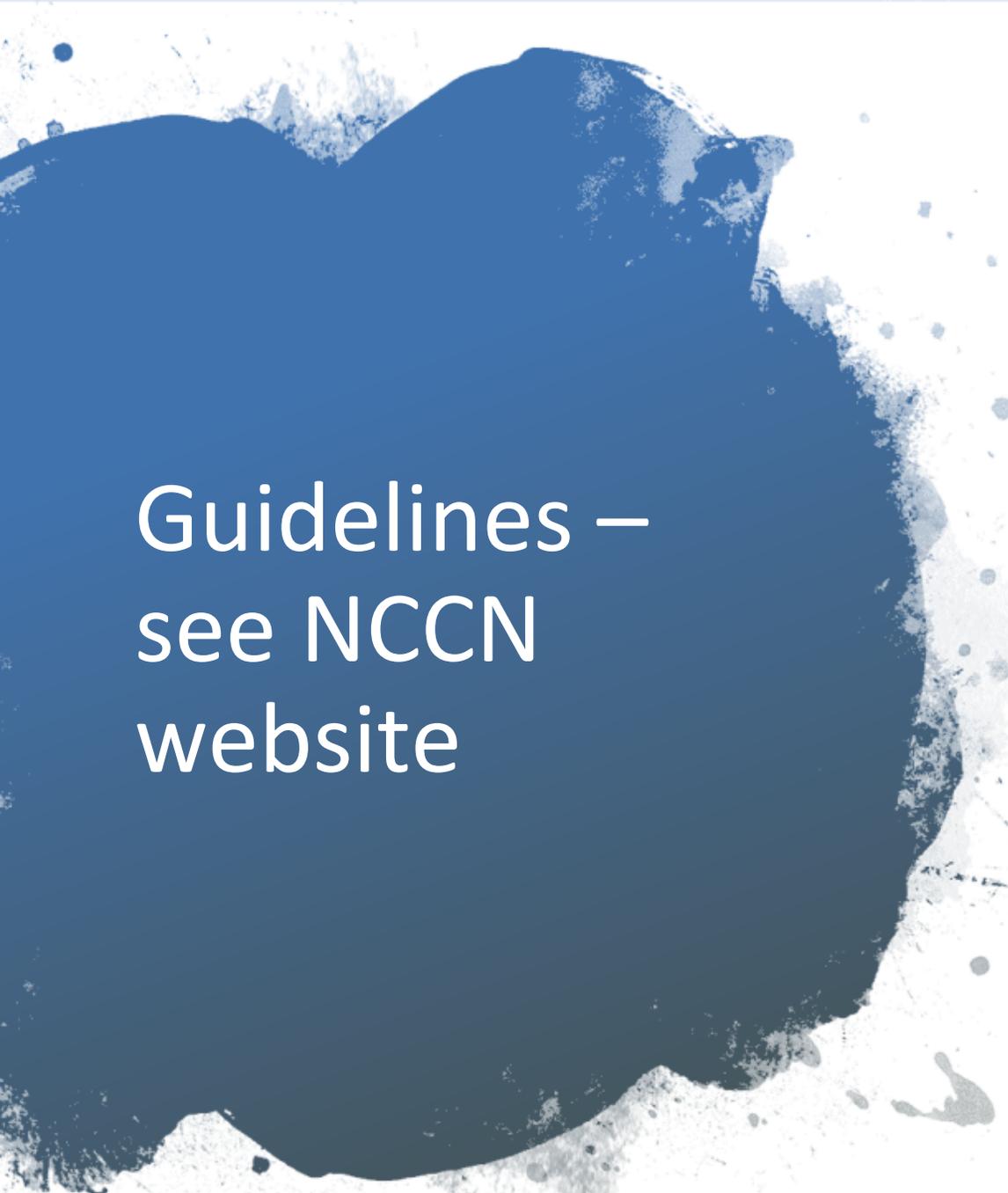
oral olanzapine 5 mg or placebo d1–4
aprepitant, palonosetron, and
dexamethasone

Less sedation than 10mg
mixed effect on sleep

Meta-analysis suggests
5mg ~ 10 mg
Chow R. PMID: 34613472

Principles

- Prophylactic therapy should be given before chemotherapy to prevent adverse outcomes
- Routes of administration: PO, PR, IV, IM
- PO route is preferred as it is most convenient /cost effective
- Often IV is needed due to inability to take PO
- Lowest maximally effective dose should be used
- Once daily dosing
- Delayed N/V therapy incorporated proactively
- Avoid using concomitant drugs in same class



Guidelines –
see NCCN
website

- In contrast to other guidelines that are often based on expert opinion - there is a significant amount of clinical trials data supporting the recommendations
- **USE THE GUIDELINES**



HIGH EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION^{h-l}

<p>DAY 1: Select treatment option A, B, or C All treatment options are category 1 and should be started before anticancer therapy^j</p>	<p>DAYS 2, 3, and 4:</p>
<p>Treatment option A (preferred), use the following combination^{m,n}:</p> <ol style="list-style-type: none"> Olanzapine 2.5–10 mg PO once daily (or bedtime)^o NK1 receptor antagonist (RA) (choose one): <ul style="list-style-type: none"> ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg intravenous (IV) once^p ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once ◊ Rolapitant 180 mg PO once^q 5-HT₃ RA (choose one)^{r,s}: <ul style="list-style-type: none"> ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg subcutaneous (SQ) once,^t or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once Dexamethasone 12 mg PO/IV once^{u,v} 	<p>Treatment option A:</p> <ul style="list-style-type: none"> • Olanzapine 2.5–10 mg PO daily (bedtime) on days 2, 3, and 4^o • Aprepitant 80 mg PO daily on days 2 and 3 (if aprepitant PO is used on day 1) • ± Dexamethasone 8 mg PO/IV daily on days 2, 3, and 4^{u,v}
<p>Treatment option B, use the following combination^m:</p> <ol style="list-style-type: none"> Olanzapine 2.5–10 mg PO once daily (or bedtime)^o Palonosetron 0.25 mg IV once Dexamethasone 12 mg PO/IV once^{u,v} 	<p>Treatment option B:</p> <ul style="list-style-type: none"> • Olanzapine 2.5–10 mg PO daily (bedtime) on days 2, 3, and 4^o
<p>Treatment option C, use the following combination^m:</p> <ol style="list-style-type: none"> NK1 RA (choose one): <ul style="list-style-type: none"> ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg IV once^p ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once ◊ Rolapitant 180 mg PO once^q 5-HT₃ RA (choose one)^{r,s}: <ul style="list-style-type: none"> ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg SQ once,^t or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once Dexamethasone 12 mg PO/IV once^{u,v} 	<p>Treatment option C:</p> <ul style="list-style-type: none"> • Aprepitant 80 mg PO daily on days 2 and 3 (if aprepitant PO is used on day 1) • Dexamethasone 8 mg PO/IV daily on days 2, 3, and 4^{u,v}

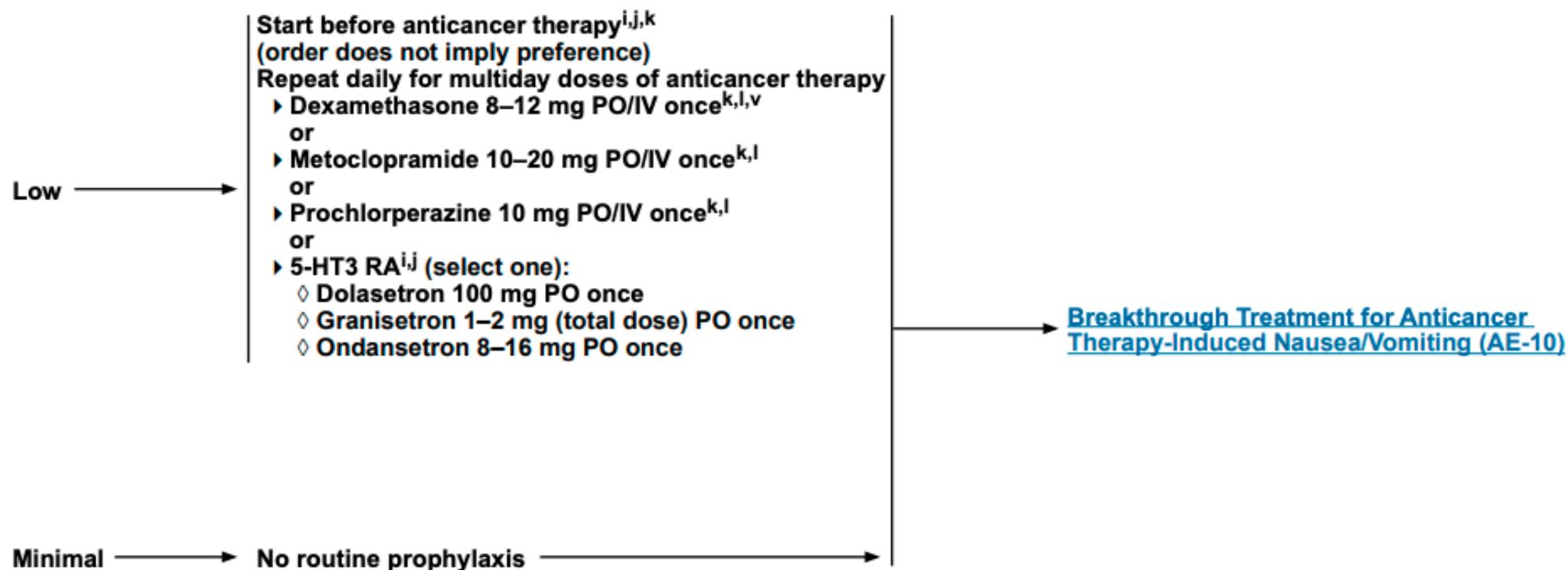


MODERATE EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION^{h-l}

DAY 1: Select treatment option D, E, or F All treatment options are category 1 and should be started before anticancer therapy ^j	DAYS 2 and 3:
<p><u>Treatment option D, use the following combination:</u></p> <p>1. 5-HT3 RA (choose one):</p> <ul style="list-style-type: none"> ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg SQ once^t (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once (preferred) <p>2. Dexamethasone 12 mg PO/IV once^{u,v}</p>	<p><u>Treatment option D:</u></p> <ul style="list-style-type: none"> • Dexamethasone 8 mg PO/IV daily on days 2 and 3^{u,v} OR • 5-HT3 RA monotherapy^x: <ul style="list-style-type: none"> ◊ Granisetron 1–2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3 ◊ Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8–16 mg IV daily on days 2 and 3 ◊ Dolasetron 100 mg PO daily on days 2 and 3
<p><u>Treatment option E, use the following combination^{n,w}:</u></p> <ol style="list-style-type: none"> 1. Olanzapine 2.5–10 mg PO once daily (or bedtime)^o 2. Palonosetron 0.25 mg IV once 3. Dexamethasone 12 mg PO/IV once^{u,v} 	<p><u>Treatment option E:</u></p> <ul style="list-style-type: none"> • Olanzapine 2.5–10 mg PO daily (bedtime) on days 2 and 3^o
<p><u>Treatment option F, use the following combination^{n,w}:</u></p> <p>1. NK1 RA (choose one):</p> <ul style="list-style-type: none"> ◊ Aprepitant 125 mg PO once ◊ Aprepitant injectable emulsion 130 mg IV once^p ◊ Fosaprepitant 150 mg IV once ◊ Netupitant 300 mg/palonosetron 0.5 mg (available as fixed combination product only) PO once ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once ◊ Rolapitant 180 mg PO once^q <p>2. 5-HT3 RA (choose one)^{r,s}:</p> <ul style="list-style-type: none"> ◊ Dolasetron 100 mg PO once ◊ Granisetron 10 mg SQ once,^t or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ◊ Palonosetron 0.25 mg IV once <p>3. Dexamethasone 12 mg PO/IV once^{u,v}</p>	<p><u>Treatment option F:</u></p> <ul style="list-style-type: none"> • Aprepitant 80 mg PO daily on days 2 and 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg PO/IV daily on days 2 and 3^{u,v}

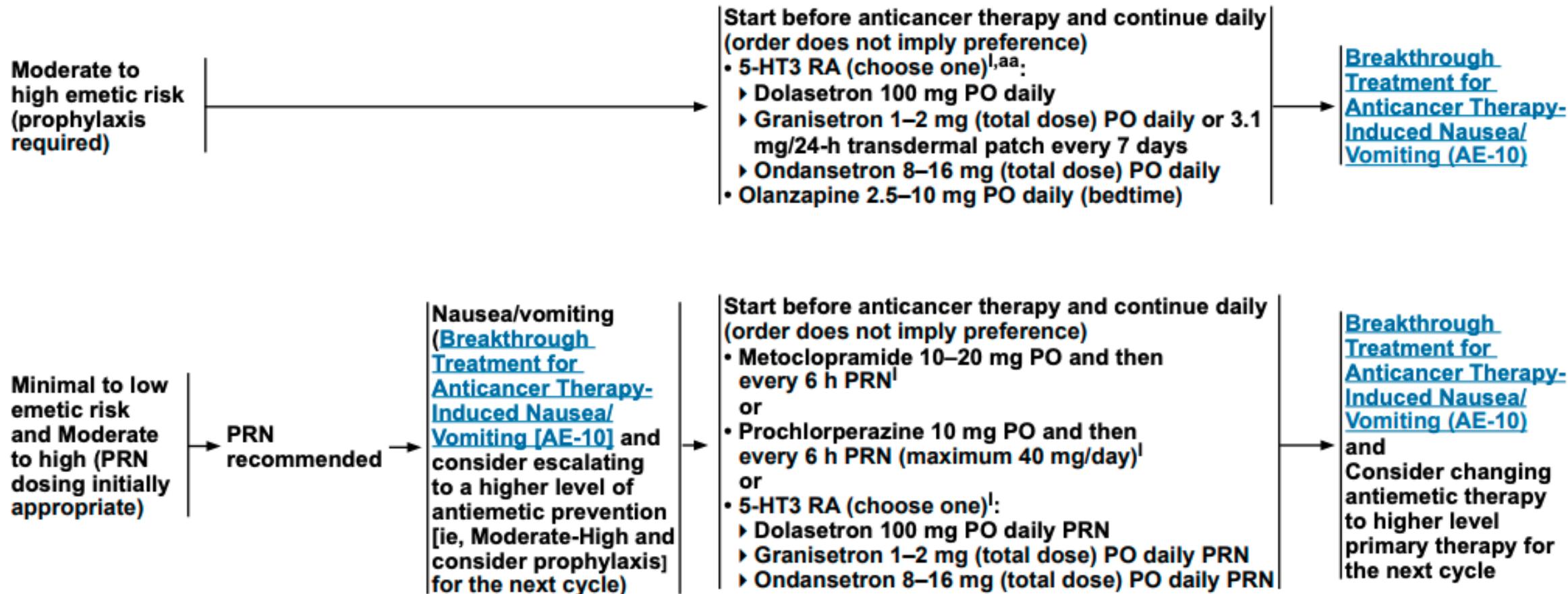


LOW AND MINIMAL EMETIC RISK PARENTERAL ANTICANCER AGENTS - EMESIS PREVENTION^{h,i,j,l}





ORAL ANTICANCER AGENTS - EMESIS PREVENTION^{i,j,bb,cc}



Breakthrough Treatment

- assess what was taken (medication reconciliation)
- add agents from a different drug class
 - Additional steroid for prolonged nausea in delayed phase
 - (don't use additional 5HT3 for 3 days post-palonosetron)
 - (5HT3 likely minimally effective in delayed phase)
- use multiple concurrent agents
- IV therapy often needed (drugs, IVF)
- round-the-clock administration
- remember this for the next cycle, assess for other causes

Consider non-CINV causes

- bowel obstruction
- constipation
- vestibular dysfunction
- brain metastases
- electrolytes, dehydration
- uremia
- other drugs (opiates)
- gastro paresis (tumor or vincristine)
- anxiety, anticipatory N/V
- Cannabis hyperemesis syndrome
- Rapid opioid withdrawal

Take Home Points

- 5-HT3 agents are the mainstay for the prevention of acute CINV in moderate to highly emetogenic regimens
- The benefit of the 5-HT3 agents (except palonoset.) in delayed CINV is debated
- Steroids significantly augment 5-HT3s and should almost always be used
- NCCN recommends avoiding steroids in immunotherapy
- Aprepitant and/or olanzapine (~5mg) are indicated for highly emetogenic chemotherapy
- High therapeutic index agents: 5HT3, NK1, olanzapine
- CW: Don't give patients starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting antiemetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting.

Erythropoiesis-Stimulating Agents (ESA)

Cancer Related Anemia

- High prevalence among cancer patients
- Multifactorial
 - Inflammatory state related to cancer
 - Treatment related myelosuppression
 - BM infiltration
 - Paraneoplastic
 - Other (bleeding, nutritional, hemolysis, congenital,...)

Workup of Anemia in Cancer Patients

- Screen for anemia in cancer patients
- Complete workup not always needed
- Consider: smear, BM, B12, folate, guaiac, Creat, retics
- EPO levels not recommended as they are not predictive of response
- Screening iron studies: ferritin, Fe, TIBC, TSAT

ESAs in solid tumor oncology

- Anemia is very common in cancer
- Linked to worse prognosis
- Worse outcomes with radiation
 - hypoxia leads to radio-resistance
- ESAs initially used in CRF, use extended to oncology
 - Reduction of transfusions, HR =0.64 in chemo patients
 - Difference between placebo was ~1 unit, NNT = 6
 - Marginal effects on QOL and fatigue
 - Utilization was quite high, but has decreased due to safety concerns

This is a controversial subject, with a vast literature

ESAs: Risks/Benefits



NCCN Guidelines Version 2.2019 Management of Cancer- and Chemotherapy-Induced Anemia

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COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RBC TRANSFUSION^h

Discuss the following risks and goals with patients when considering anemia treatment options:

	ESA in the Cancer Setting	RBC Transfusion
Risks	<ul style="list-style-type: none">• Increased thrombotic events• Possible decreased survival• Time to tumor progression shortened	<ul style="list-style-type: none">• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury)• Transfusion-associated circulatory overload (TACO)• Virus transmission (eg, hepatitis, HIV)• Bacterial contamination• Iron overload• Increased thrombotic events• Possible decreased survival• Alloimmunization• Increased risk of poor response to future platelet transfusions due to HLA immunization
Goals	<ul style="list-style-type: none">• Transfusion avoidance• Gradual improvement in anemia-related symptoms	<ul style="list-style-type: none">• Rapid increase of Hb and hematocrit levels• Rapid improvement in anemia-related symptoms

[See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects \(ANEM-A\)](#)

When considering ESAs:

- Discuss the risks of ESAs with patients including the potential for tumor growth, death, blood clots, and serious heart problems.
- Refer patients to the following medication guides for more information on the benefits and risk of ESAs: [Epoetin Alfa Medication Guide](#), [Epoetin Alfa-epbx Medication Guide](#) and [Darbepoetin Alfa Medication Guide](#)

When considering RBC transfusion, see AABB Clinical Practice Guidelines: Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. *Transfusion* 2016;56:2627-2630.

Iron deficiency

EVALUATION OF IRON DEFICIENCY^p

Iron studies:
Iron panel (serum
iron, total iron-binding
capacity, serum ferritin)^f

IRON STATUS

Absolute iron deficiency^q
(ferritin <30 ng/mL AND
transferrin saturation
[TSAT] <20%)

Functional iron deficiency
in patients receiving ESAs^{r,s}
(ferritin 30–500 ng/mL AND
TSAT <50%)

Possible functional iron
deficiency^{r,s,t} (ferritin >500–
800 ng/mL AND TSAT <50%)

No iron deficiency
(ferritin >800 ng/
mL OR TSAT ≥50%)

MANAGEMENT

Consider IV or oral
iron supplementation

Hb increases
after 4 wks

No Hb increase
after 4 wks

Periodic evaluation (repeat
ferritin and TSAT)

See pathway below for
functional iron deficiency

Consider IV iron supplementation^{u,v}
with erythropoietic therapy

See [Discussion](#) for clinical
examples of iron status

No iron supplementation needed
or
Consider IV iron supplementation for select patients

IV or oral iron supplementation is not needed

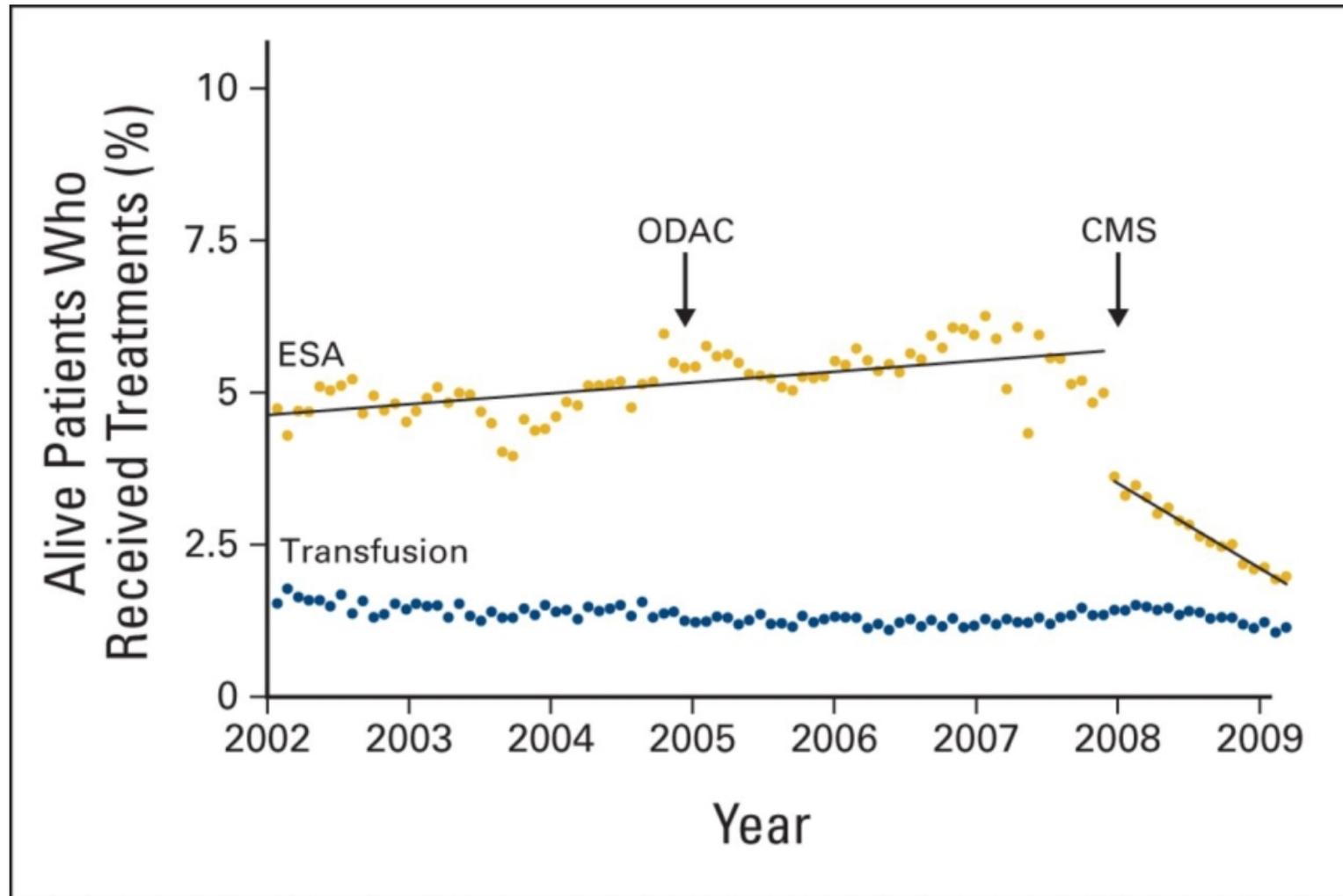
[Parenteral Iron Preparations \(ANEM-B\)](#)

^f The ferritin value indicating iron deficiency is laboratory-specific. In general,

Recommendations

- No use of ESA for anemia not associated with chemotherapy
- For chemotherapy related anemia, weigh risks/benefits
- Start Hgb < 10, goal = avoid transfusion, increase < 1gm/2w
- CMS start Hgb < 10, DC for >10
- FDA indications and dosing should be used, NCCN lists alternative regimens
- 5 of 6 studies show that Fe supplementation in absolute or functional Fe deficiency improves response to ESAs

Percentage of patients with cancer who received erythropoiesis-stimulating agents (ESAs) per month in relation to regulatory changes.



Myeloid Growth Factors

Myeloid Growth Factors

- Neutropenia is a common DLT of chemotherapy
- Febrile neutropenia (FN) results in hospitalization, IV antibiotic use, decreased QOL, and morbidity
- FN risk is highest with first two cycles of a regimen
- Neutropenia may result in reductions in dose-density and intensity which can compromise outcomes
- This all can be reduced with use of myeloid CSFs

Myeloid CSFs

- Reduce risk (by ~50% for FN), severity and duration of neutropenia
- Cost-benefit threshold is now at 20% risk of FN, previously was at 40%
- Many common regimens have 25-40% FN risk in treatment naïve patients

Risk of FN – chemotherapy

- Risk is hard to define precisely
- Published trials are informative
- Guidelines (NCCN) have been published which estimate risk for regimens

Patient risk factors for neutropenia

Treatment-related

- Previous history of severe neutropenia with similar chemotherapy
- Type of Chemotherapy (anthracyclines)
- Planned relative dose intensity > 80%
- Preexisting neutropenia (< 1000) or lymphocytopenia
- Extensive prior chemotherapy
- Concurrent or prior radiation therapy to marrow containing bone

Patient-related

- Age (> 65 y)
- Female gender
- Poor performance status (ECOG \geq 2)
- Poor nutritional status (eg, low albumin)
- Decreased immune function

Cancer-related

- Bone marrow involvement with tumor
- Advanced or uncontrolled cancer
- Elevated Lactate Dehydrogenase (Lymphoma)
- Leukemia
- Lymphoma
- Lung cancer

Conditions associated with risk of serious infection

- Open wounds
- Active tissue infection

Comorbidities

- COPD
- Cardiovascular disease
- Liver disease (elevated bilirubin, alkaline phosphatase)
- Diabetes mellitus
- Low baseline hemoglobin

Use of myeloid CSFs

- Risk of FN
 - >20% recommended
 - 10-20% consider
 - <10% generally not recommended
 - CW: Don't use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.
- Also consider intent of treatment: curative, adjuvant, palliative
- Prior FN is an indication for CSFs
- Prior FN w/CSF-> dose reduction or change regimen
- Do not use with chemoradiation
- (antibiotics not recommended)



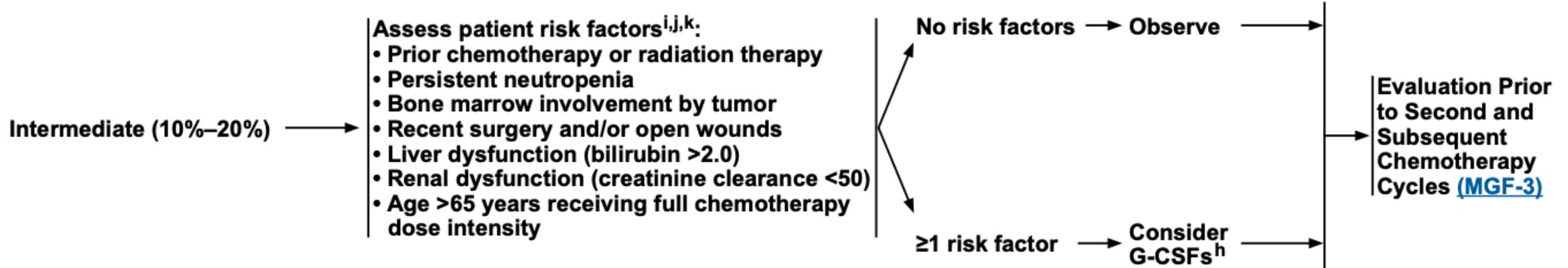
NCCN Guidelines Version 1.2025

Hematopoietic Growth Factors

OVERALL FEBRILE NEUTROPENIA^e RISK

PATIENT RISK FACTORS ASSESSMENT

PROPHYLACTIC USE OF G-CSFs FOR FEBRILE NEUTROPENIA



Myeloid CSF regimens

- Filgrastim
 - 5mcg/kg/d rounded to 300 or 480mcg
 - Start 1-3 days after chemo
 - Treat through post-nadir recovery
- Tbo-filgrastim, filgrastim-sndz, other biosimilars
- Pegfilgrastim, other biosimilars, OnPro[®]
 - 6mg/cycle
 - Start 1-3 days after chemo
 - Data for q3wk regimens, phase II data for q2wk
 - Dosing on day 1 safe, but less efficacious*
 - NCCN recommends administration on day 2

*Lyman, GH. Support Care Cancer (2017) 25:2619–2629

Adverse Effects

- Bone pain (common)
- Allergic reactions
- ARDS
- Splenic rupture (transplant setting)
- Precipitate sickle cell crisis
- MDS/AML* (increased AR 0.4%, RR 1.9)
- Cutaneous vasculitis (Sweet's syndrome)

Bone Supportive Care

Skeletal Morbidity

- Cancer treatment induced bone loss
 - Androgen deprivation
 - Estrogen deprivation
 - Corticosteroids, TSH suppression
 - These will not be discussed further
- Bone metastases
 - Common in many cancer
 - Lung, breast, and prostate are most common

Measuring Skeletal Morbidity

- “Skeletal related event” – SRE
 - Fracture, spinal cord compression
 - Need for surgery or radiation
 - (some definitions) hypercalcemia
- QOL and pain are other outcomes of interest
- SREs are quite common, estimates are > 50% of metastatic breast cancer patients will have a SRE

Bisphosphonates

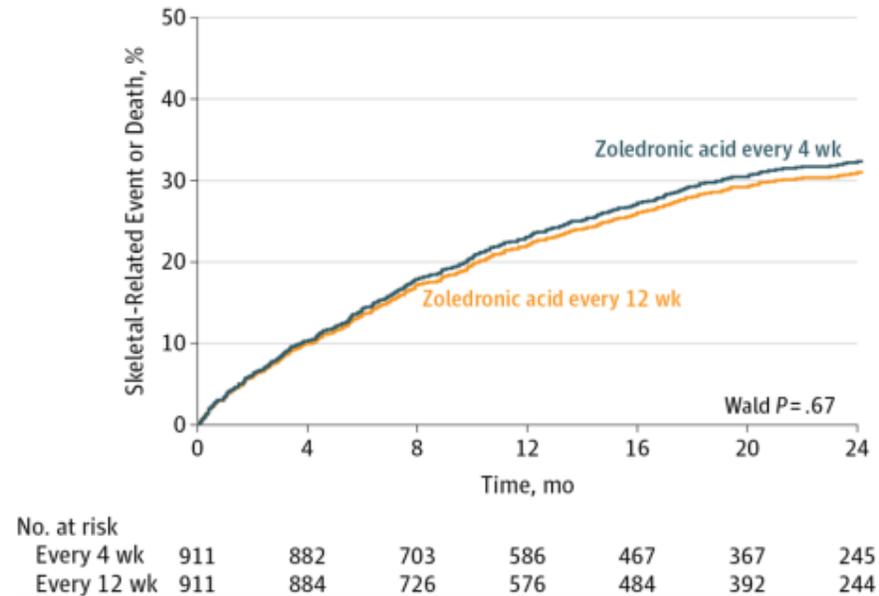
- Analogs of pyrophosphate – a major constituent of bone
- Decrease bone resorption and increase mineralization by inhibiting osteoclast activity
- Induce apoptosis in osteoclasts
- Zoledronic acid (ZA) and pamidronate are potent bisphosphonates

Bisphosphonates in solid tumors with established bone metastases

- Positive data is primarily for zoledronic acid (ZA)
- ZA vs. placebo in AR-prostate cancer
 - Incidence of SRE 38% vs. 49% median FU 2yrs
 - TTE was 488 vs. 321 days, benefit in pain control
- ZA vs. placebo in solid tumor
 - (no breast/prostate, mostly NSCLC)
 - Incidence of SRE 38% vs. 47%
 - TTE was 230 vs. 163 days

From: **Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases** A Randomized Clinical Trial

JAMA. 2017;317(1):48-58. doi:10.1001/jama.2016.19425



Cause-Specific Cumulative Incidence of Skeletal-Related Events There were 256 patients with skeletal-related events in the zoledronic acid every 4-week dose group and 246 patients in the every 12-week dose group (hazard ratio, 0.96 [95% CI, 0.81-1.15]).

Denosumab

- Monoclonal antibody targeting the RANKL which is involved in osteoclast formation and activation
- Has indications for osteoporosis and prevention of SREs in solid tumors
- Denosumab does not have renal toxicity
- Given as 120mg SQ injection q 4 weeks
- Emerging data for q 12 weeks, Ongoing trial: NCT02051218
- Goodrx: \$2400 vs \$33 for ZA

Denosumab efficacy

- All have ZA as comparator arm
- Three positive trials: breast, AR-prostate, “other”
- Denosumab vs. ZA
- Other (N=1176) MM and solid tumors (not breast or prostate), 40% were NSCLC
 - TTE 20.6m vs. 16.3 mo.
 - P=0.03, but 0.06 after correction for multiple comparisons

ONJ - osteonecrosis of the jaw

- Presents as infection with exposed necrotic maxillary or mandibular bone
- Risks: poor dental hygiene, dental extractions/implants, chemotherapy?, anti-angiogenics?
- Incidence is ~2% for both ZA and denosumab
- Most patients who get ONJ have a risk factor (~80%)
- “Dental” exam prior to initiation
- Avoid invasive dental procedures

Comparison

Denosumab

- Expensive
- Monthly
- Ok in renal dysfunction
- Mildly improved SRE
- Rebound vertebral fractures after DC
- Hypersensitivity, neutralizing Abs
- Mild increase in infections (skin, UTI)

ZA

- Cheap
- Q 3 month
- Avoid if CrCl < 30, dose adjust; potential for renal injury
- Acute phase reaction – flu like ~50%
- conjunctivitis, uveitis, scleritis, and orbital inflammation
- Afib/flutter , stroke – RR~1.3 in SEER
- MSK pain

Common to both: hypocalcemia , ONJ, atypical fractures

Conclusions

- Use agents in patients with established bone metastases
- Aggregate data favors denosumab over ZA, but cost is high
- Among bisphosphonates ZA is the preferred agent
- Screen for ONJ risk factors prior to use
- Adverse events are similar between agents
- Supplement Ca, D, replete if deficient prior to therapy

Fatigue

- High symptom burden among cancer patients
- Some nihilism regarding treatment
- I will focus on NCCN guidelines and trials data
- “Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”

Sources – NCCN Guidelines and Cancer-related fatigue; UpToDate

Fatigue Evaluation

- Medications
- Pain
- Emotional distress -depression
- Anemia
- Sleep disturbance
- Comorbidities – endocrine disorders, organ dysfunction
- Assessment on 0-10 scale

Interventions: non – pharmacologic

- Different interventions for different milestones in cancer treatment
- Management strategies (delegation, prioritize)
- physical activity (cat 1)
- massage therapy, CBT, educational therapies (cat 1)
- Sleep hygiene – structure, naps

Pharmacologic Interventions

- Stimulants – methylphenidate
 - Modafinil
 - Corticosteroids
 - Ginseng
-
- Overall evidence is weak or mixed for these interventions

Methylphenidate

- Of 8 RCTs, only 2 have demonstrated benefit
- Most rigorous studies were negative
- Trials were small and populations heterogeneous
- Suggestion of greater benefit with
 - Higher levels of fatigue
 - More advanced disease
 - Opioid related fatigue
 - Higher dose

Simulants for fatigue

- Cancer related fatigue is not a lawful indication for use of stimulants under Washington state law WAC 246-945-045
- This is a class C felony
- Professional Guidelines
- ESMO panel 6/9 do not Rx; 3/9 psychostimulants could be considered in selected patients and their usefulness and safety should be evaluated after a very short time period - similar comments applied to ginseng and mistletoe
- NCCN recommends only after ruling out other treatment or disease specific morbidities while acknowledging use is investigational without agreed upon dose or schedule

Modafinil

- “Wake-promoting” agent for narcolepsy
- Initial pilot studies were encouraging
- Subsequent studies did not show overall benefit
 - N=631 evaluable, any level of fatigue, only patients with score ≥ 7 showed benefit
 - N=160 in ITT, NSCLC no benefit over placebo

Corticosteroids

- Studied in terminal stage of cancer
- Long-term side effects limit utility in patients with longer life expectancy
- N=84 RCT of advanced cancer patients with fatigue(≥ 4) and high symptom burden, dexamethasone 4mg bid vs. placebo
- Improved QOL and fatigue scores

J Clin Oncol. 2013 Sep 1;31(25):3076-82.

Ginseng

- N=364 cancer patients with curative intent therapy and fatigue(≥ 4) , RCT of ginseng 2000mg vs. PCO
- Improved fatigue at 8 week (but not 4 week)
- No discernable toxicities
- Potential for drug interactions, inhibitor of CYP3A4

J Natl Cancer Inst. 2013 Aug 21;105(16):1230-8.

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Common side effect of many agents
 - Most common in breast and colon cancer
 - Platins, taxanes, vincas, bortezomib
- Can be dose-limiting
- Potential for significant impact on QOL

CIPN

- Prevention – despite some reports demonstrating benefit, NO agent has been useful for prevention of CIPN
- Possible beneficial effect of limb cooling/compression/exercise
- Prevention strategies are dose reduction, dose delays, and treatment breaks
- Bortezomib: Weekly vs. 2x/week and SQ vs IV is preferred
- Treatment – the only agent that has demonstrated efficacy is duloxetine
- 59% vs 38% (PCO) reported pain decrease
- Difference in decrease of pain was modest: 0.7 on a 1-10 scale
- RCT: Smith EM. JAMA. 2013 Apr 3;309(13):1359-67. PMID: 23549581

Oxaliplatin-induced acute neuropathy

- Unique toxicity: oral thermal hyperalgesia (OTH) – form of acute neuropathy due to disrupted voltage-gated Na⁺ channels → hyperexcitability of cold-sensing sensory nerves
 - Single-center RCT evaluated efficacy of oral cryotherapy (ice chips) during oxaliplatin infusion and found lower rates of oral symptoms after first treatment cycle with cryotherapy (Bauman B, et al. *J Natl Compr Canc Netw* 2019;17(4):358-364)
- Oxaliplatin-induced acute peripheral neuropathy (PN) often provoked by exposure to cold, characterized by paresthesia/dysesthesia in hands/feet
 - Oxaliplatin can lead to chronic PN similar to cisplatin, characterized by sensory changes
 - Phase II single-center RCT evaluated efficacy of hand/foot cooling 30 minutes before, during oxaliplatin infusion, and until 30 min after end and found lower incidence of grade 2+ OIPN at 12 and 24 weeks
 - Strong reduction in severity and duration of both peripheral ($p < 0.0001$) and pharyngeal ($p = 0.0005$) acute neuropathy (Coolbrandt A, et al. *ESMO Open* 2023;8(2):101205.
- Hypothesized that cooling may lower core temperature and result in secondary peripheral vasoconstriction → decreased exposure/toxicity

Exercise Therapy on CIPN

- Potential association between physical activity and recovery of neurological function vis-à-vis CIPN
- Systematic reviews and metaanalyses have found exercise may be beneficial for improving QOL and CIPN symptoms
 - Caution in interpretation: bias, majority retrospective (only 1 RCT)
 - Pts with ovarian cancer (Konuma M, et al. *Gynecol Oncol* 2025;192:155-162)
 - Pts with breast and colorectal (Nakagawa N, et al. *Front Neurol* 2024;15:1346099)
- ASCO also provides recommendations for patients undergoing active treatment with curative intent with regular aerobic and resistance exercise to mitigate SE of cancer treatment (Ligibel JA, et al. *J Clin Oncol* 2022;40(22):2491-2507.)

Cancer Cachexia

- Pharmacologic interventions:
- Olanzapine 2.5-5 mg daily has emerged as preferred option
- RCT looked at >5% wt gain (60% vs 9% PCO) PMID 36977285
- corticosteroids and progesterone analogs have demonstrated benefit
- Increased appetite, modest weight gain
- No effect on survival or overall QOL

Treatment of Cancer Cachexia

Olanzapine

For patients with short life expectancy (~weeks) dexamethasone (4mg daily)

- Side effects: myopathy, Cushingoid, PUD

Megestrol 400-800mg daily for longer term

- Side effects: edema, VTE, increased mortality with doses >800mg/d
- Effect is weak, 16% of patients with >15# gain

No benefit of dronabinol in RCTs

Treatment of Cancer Cachexia: On the Horizon

- Growth differentiation factor 15 (GDF-15) – stress-induced cytokine binding to glial cell-derived neurotrophic factor family receptor alpha-like protein (GFRAL)
- GDF-15-GFRAL pathway modulates anorexia and body-weight regulation, thought to be implicated with cachexia
- Ponsegromab – binds to circulating GDF-15, inhibiting interaction with GFRAL receptor
- Phase II, randomized trial examined pts with cachexia and elevated serum GDF-15 on ponsegromab (100, 200, 400 mg SUBQ every 4 weeks x3 doses) vs placebo and at 12 weeks, found greater weight gain than placebo and improved appetite/cachexia symptoms with the 400 mg dose vs placebo (Groarke JD, et al. *N Engl J Med* 2024;391:2291-303.)
 - AE: well-tolerated; (ponsegromab % v placebo %): diarrhea (8 v 18), anemia (8 v 11), hypokalemia (8 v 9), nausea (4 v 16), vomiting (5 v 13)

Sources for further study

- ASCO Guidelines: Supportive Care and Treatment Related Issues; Patient and Survivor Care
- NCCN Guidelines for Supportive Care
- ESMO Clinical Practice Guidelines: Supportive and Palliative Care
- MASCC, Multinational Association for Supportive Care in Cancer
- UpToDate – multiple topics covered



Thank you

UW Medicine

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) are posted with the latest update date and version number.

Adult Cancer Pain

Version: 2.2025

Antiemesis

Version: 2.2025

Cancer-Associated Venous Thromboembolic Disease

Version: 2.2025

Cancer-Related Fatigue

Version: 2.2025

Distress Management

Version: 2.2025

Hematopoietic Cell Transplantation

Version: 3.2025

Hematopoietic Growth Factors

Version: 1.2025

Management of Immunotherapy-Related Toxicities

Version: 1.2025

Palliative Care

Version: 2.2025

Prevention and Treatment of Cancer-Related Infections

Version: 1.2025

Smoking Cessation

Version: 1.2025

Survivorship

Version: 2.2025