Supportive Care

Keith Eaton, MD, PhD

2021

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
- Supportive Care, Survivorship, and Communication = 10% 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, 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

Am J Health-Syst Pharm. 1999;56:729. J Clin Oncol. 1999;17:2971.

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[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c,d]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis) [b,c,d]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC[e] <4 • Carmustine[e] ≤250 mg/m² • Clofarabine • Cyclophosphamide[e] ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[e]	• Daunorubicin[e] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[e] <60 mg/m² • Enfortumab vedotin-ejfv • Epirubicin[e] ≤90 mg/m² • Fam-trastuzumab deruxtecan • Idarubicin[e] • Ifosfamide[e] <2 g/m² per dose • Interferon alfa ≥10 million IU/m²	• Irinotecan[e] • Irinotecan (liposomal) • Melphalan • Methotrexate[e] ≥250 mg/m² • Oxaliplatin[e] • Temozolomide • Trabectedin[e]

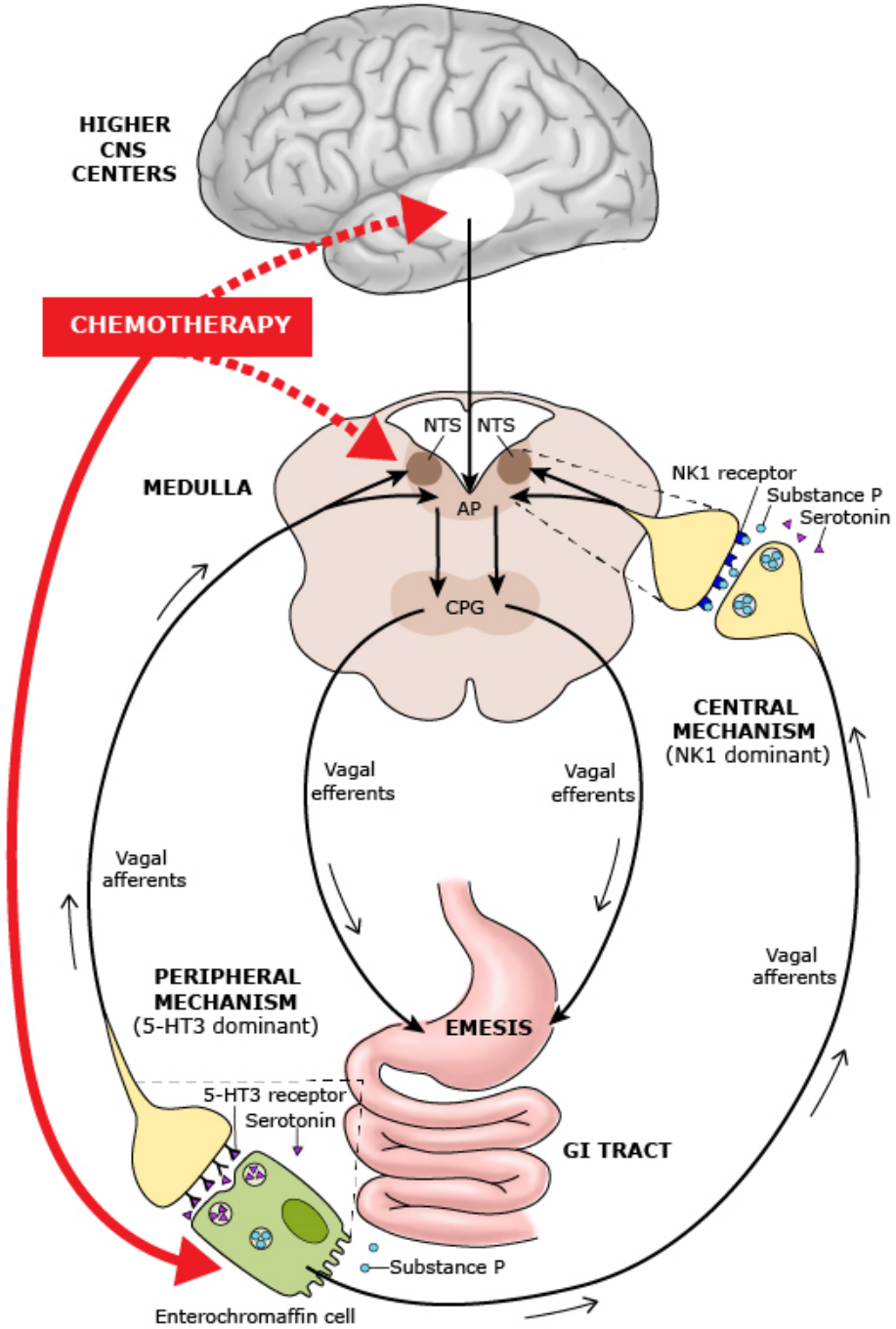
EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Low emetic risk (10%–30% frequency of emesis)[b,d,f]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/ m^2 • Amifostine ≤300 mg/m^2 • Arsenic trioxide • Axicabtagene ciloleucel[g] • Belinostat • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Copanlisib	• Cytarabine (low dose) 100–200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Gemtuzumab ozogamicin • Inotuzumab ozogamicin • Ixabepilone	• Methotrexate >50 mg/m^2 - <250 mg/m^2 • Mitomycin • Mitoxantrone • Mogamulizumab • Moxetumomab • Necitumumab • Olaratumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin	• Pemetrexed • Pentostatin • Polatuzumab vedotin • Pralatrexate • Romidepsin • Tagraxofusp • Talimogene laherparepvec • Thiotepa • Tisagenlecleucel[g] • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b,d,f]	• Alemtuzumab • Atezolizumab • Avelumab • Asparaginase • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cetuximab • Cemiplimab • Cladribine • Cytarabine <100 mg/m^2 • Daratumumab	• Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab • Elotuzumab • Fludarabine • Ipilimumab • Methotrexate ≤50 mg/m^2 • Nelarabine • Nivolumab	• Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pembrolizumab • Pertuzumab • Ramucirumab • Rituximab • Rituximab and hyaluronidase human injection, for subcutaneous use	• Siltuximab • Temsirolimus • Trastuzumab • Trastuzumab and hyaluronidase injection, for subcutaneous use • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Support Care Cancer 2011;19:S43-S47.

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Moderate to high emetic risk[b,z] (≥30% frequency of emesis)	• Altretamine • Avapritinib • Binimetinib • Busulfan (≥4 mg/d) • Ceritinib • Crizotinib	• Cyclophosphamide (≥100 mg/m²/day) • Dabrafenib • Enasidenib • Encorafenib • Estramustine	• Etoposide • Lenvatinib • Lomustine (single day) • Midostaurin • Mitotane	• Niraparib • Olaparib • Procarbazine • Rucaparib • Selinexor • Temozolomide (>75 mg/m²/day)
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Abemaciclib • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Axitinib • Bexarotene • Brigatinib • Bosutinib • Busulfan (<4 mg/day) • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide (<100 mg/m²/day) • Dacomitinib • Dasatinib	• Duvelisib • Entrectinib • Erdafitinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib • Ixazomib • Ivosidenib • Lapatinib • Larotrectinib • Lenalidomide	• Lorlatinib • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Neratinib • Osimertinib • Palbociclib • Panobinostat • Pazopanib • Pomalidomide • Ponatinib • Regorafenib • Ribociclib • Ruxolitinib • Sonidegib • Sorafenib	• Sunitinib • Talazoparib tosylate • Temozolomide (≤75 mg/m²/day)[aa] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Trifluridine/tipiracil • 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

- $5HT_3$ 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/NK_1 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 ($5HT_3$) 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, $5HT_3$ release was not found in delayed phase of CINV
- Palonosetron has efficacy for prevention of delayed emesis, but role of other $5HT_3$ is debated

5-HT3 receptor antagonists

- ondansetron (1991), granisetron, dolasetron, palonsetron (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

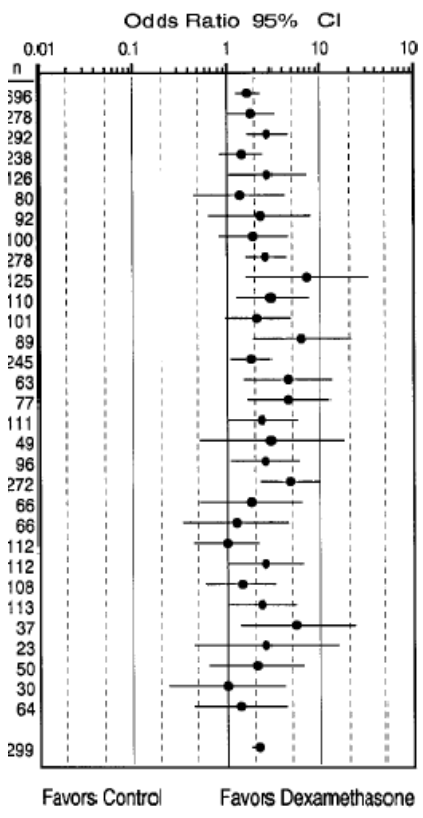
Palonsetron

- pharmacologically distinct
- 100-fold higher binding affinity for 5-HT3R
- T ½ ~ 40 hours
- As effective as traditional 5-HT3 agents for acute CINV (single dose)
- Superior in preventing delayed emesis (single dose)

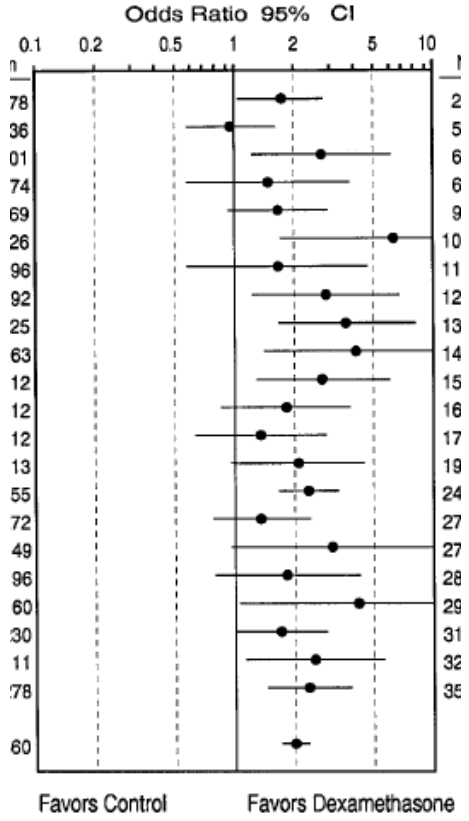
Dexamethasone addition to 5HT3

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

Acute Phase



Delayed Phase



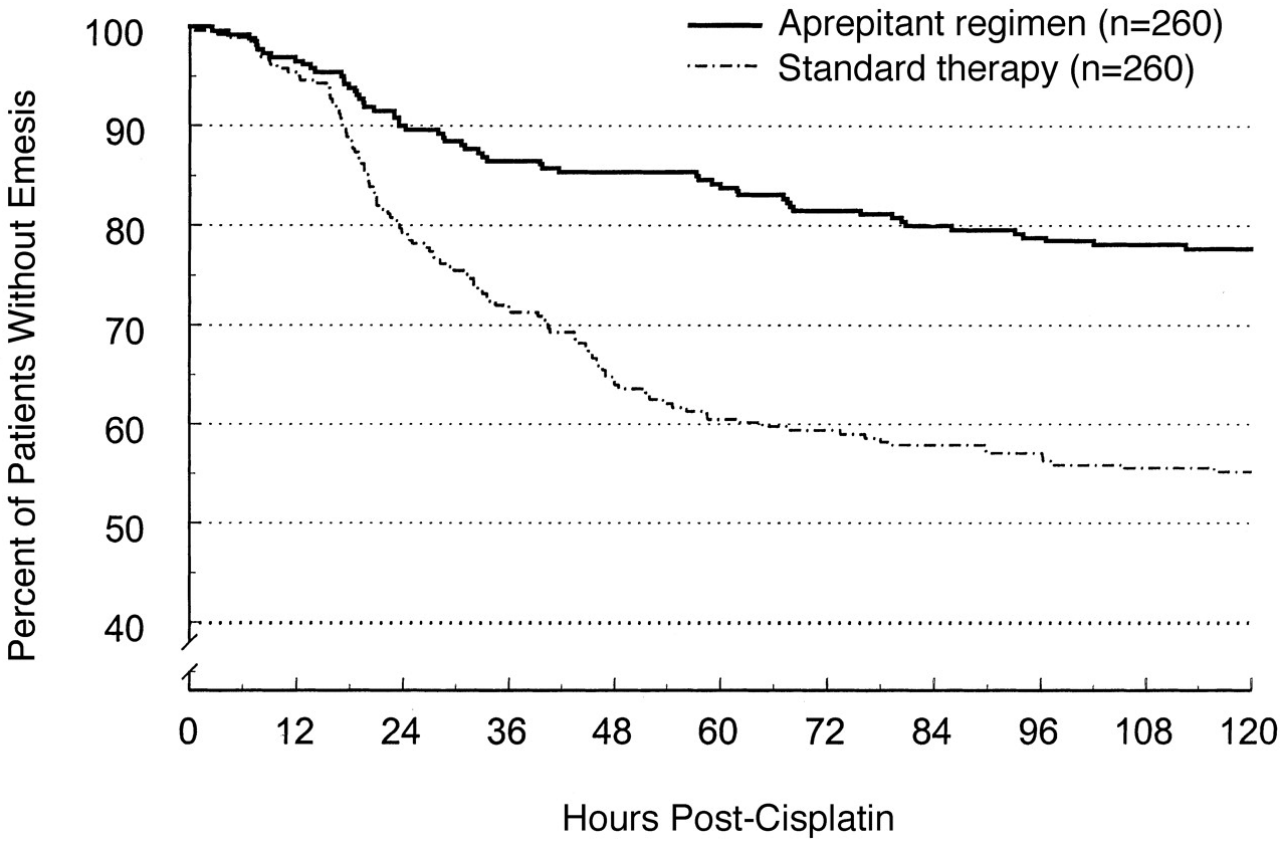
(side note – dexamethasone induced hiccup -> prednisone)

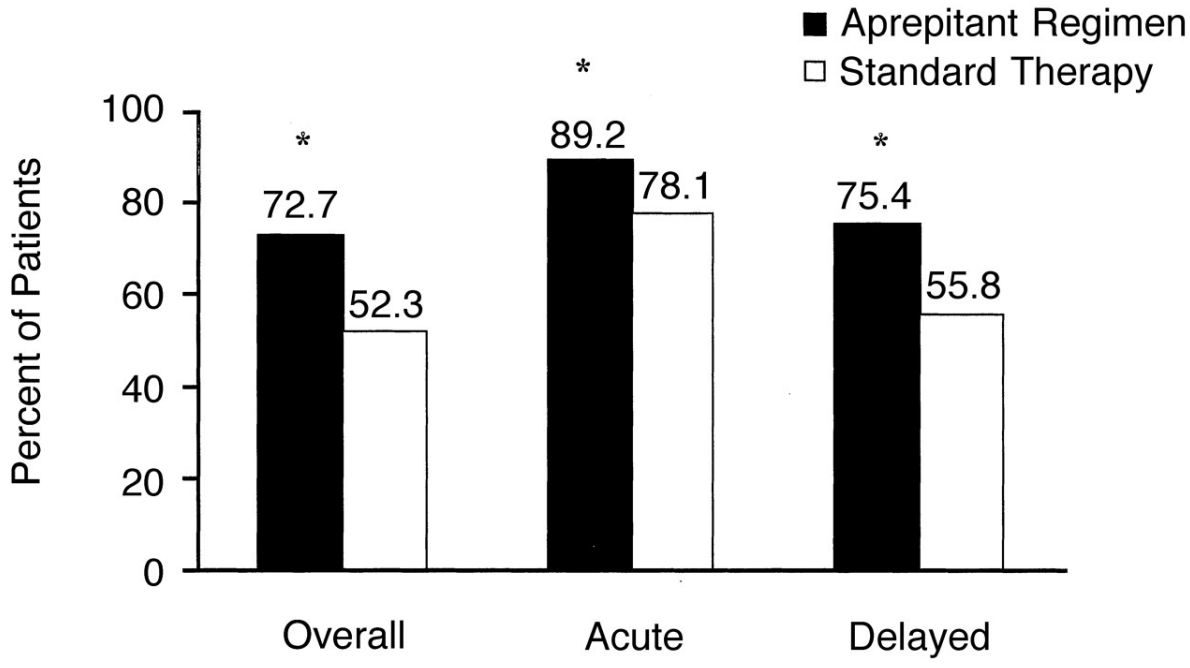
Ioannidis et al. JCO. PMID 11013282

Substance P / Neurokinin Receptors Aprepitant/fosaprepitant

- 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 solitarus (NTS) and area postrema
- Also located in the GI tract
- Beneficial in delayed > acute CINV, but use is in prevention
- New non-polysorbate-80 IV formulation for aprepitant

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





Standard therapy – ondansetron d1, dexamethasone d1-4

Hesketh et al. JCO 2003;21:4112-4119

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

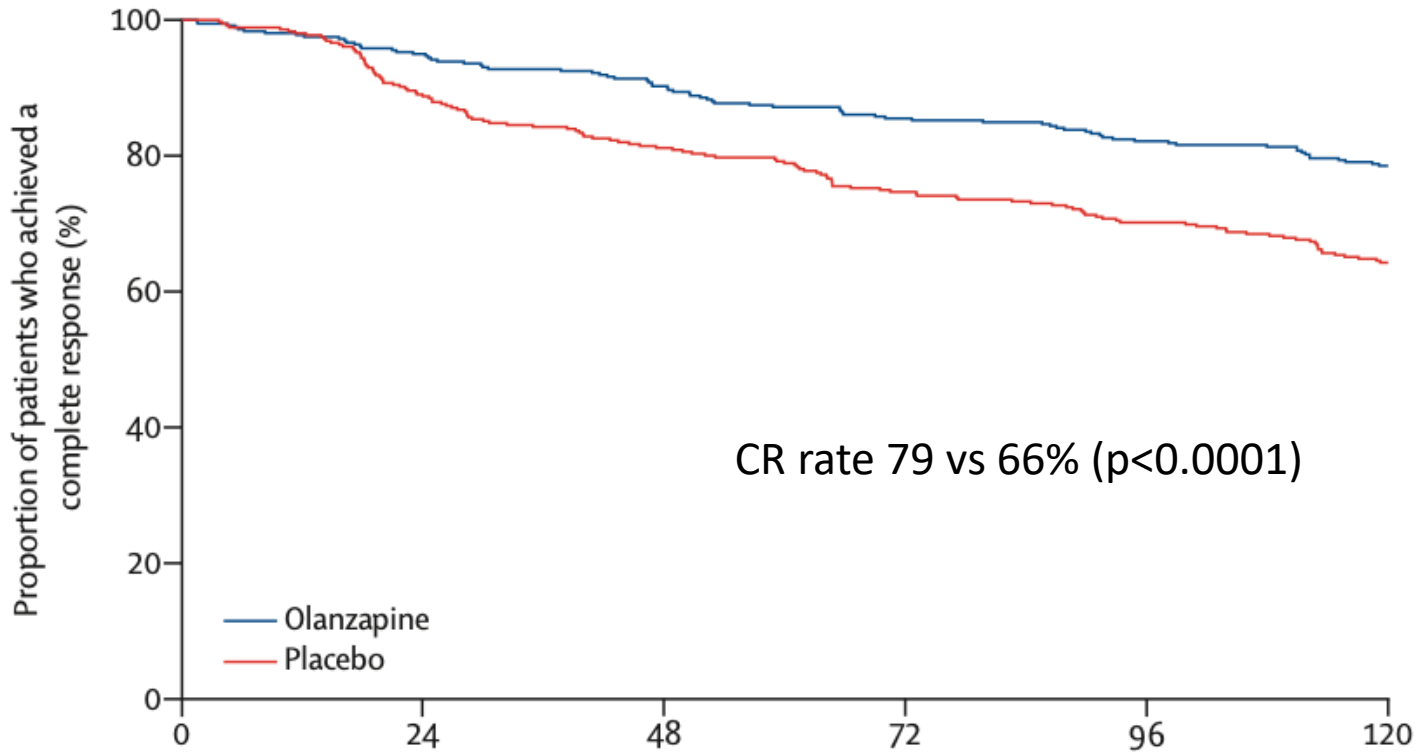
	CR Rate=no emesis or rescue(%)		No nausea (%) = primary endpt	
	Olanz	PCO	Olanz	PCO
0-24 hr	86	65	74	55
0-120 hr	64	40	37	22

All $P < 0.01$, N= 380

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

Navari RM et al. NEJM 2016: 375: 134-142

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



CR rate 79 vs 66% (p<0.0001)

Number at risk						
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

Hashimoto H. Lancet Oncol. 2020;21(2):242-249

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,i,j,k,l]

DAY 1: Select treatment option A, B, or C All treatment options are category 1 and should be started before chemotherapy[j]	DAYS 2, 3, 4:
Treatment option A (preferred), use the following combination: • Olanzapine 5–10 mg PO once[m,n] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ 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 chemotherapy. ▸ 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]	Treatment option A: • Olanzapine 5–10 mg PO daily on days 2, 3, 4[m] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4
Treatment option B, use the following combination: • Olanzapine 5–10 mg PO once[m] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option B: • Olanzapine 5–10 mg PO daily on days 2, 3, 4[m]
Treatment option C, use the following combination: • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ 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 chemotherapy. ▸ 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]	Treatment option C: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4

MODERATE EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select treatment option D, E, or F. All treatment options are category 1 and should be started before chemotherapy:[j]	DAYS 2, 3:
Treatment option D, use the following combination: • 5-HT3 RA (choose one): ▸ 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 chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once (preferred) • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option D: • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[w]: ▸ 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, 3 ▸ Dolasetron 100 mg PO daily on days 2, 3
Treatment option E, use the following combination:[x] • Olanzapine 5–10 mg PO once[m] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option E: • Olanzapine 5–10 mg PO daily on days 2, 3[m]
Treatment option F, use the following combination:[x] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once[p] ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ 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 chemotherapy. ▸ 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]	Treatment option F: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3

LOW AND MINIMAL EMETIC RISK PARENTERAL ANTICANCER AGENTS - EMESIS PREVENTION[h,i,j,l]

Low →

Start before chemotherapy[i,j,y]
Repeat daily for multiday doses of chemotherapy

- **Dexamethasone 8–12 mg PO/IV once[l,y]**
  or
- **Metoclopramide 10–20 mg PO/IV once[l,y]**
  or
- **Prochlorperazine 10 mg PO/IV once[l,y]**
  or
- **5-HT3 RA[l,y] (select one):**
  - ◊ **Dolasetron 100 mg PO once**
  - ◊ **Granisetron 1–2 mg (total dose) PO once**
  - ◊ **Ondansetron 8–16 mg PO once**

→ Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)

Minimal → **No routine prophylaxis** →

ORAL CHEMOTHERAPY - EMESIS PREVENTION[i,j,bb,cc]

High to moderate emetic risk →

Start before chemotherapy and continue daily (order does not imply preference)[y]
- **5-HT3 RA (choose one):[l]**
  - **Dolasetron 100 mg PO daily**
  - **Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-h transdermal patch every 7 days**
  - **Ondansetron 8–16 mg (total dose) PO daily**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)**

Low to minimal emetic risk → **PRN recommended** → **Nausea/ vomiting** →

Start before chemotherapy and continue daily (order does not imply preference)[y]
- **Metoclopramide 10–20 mg PO and then every 6 h PRN[l]**

  or
- **Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/day)[l]**

  or
- **5-HT3 RA (choose one):[l]**
  - ◊ **Dolasetron 100 mg PO daily PRN**
  - ◊ **Granisetron 1–2 mg (total dose) PO daily PRN**
  - ◊ **Ondansetron 8–16 mg (total dose) PO daily PRN**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)**
and
Consider changing antiemetic therapy to higher level primary therapy for the next cycle

Breakthrough Treatment

- assess what was actually 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 palonset.) 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)

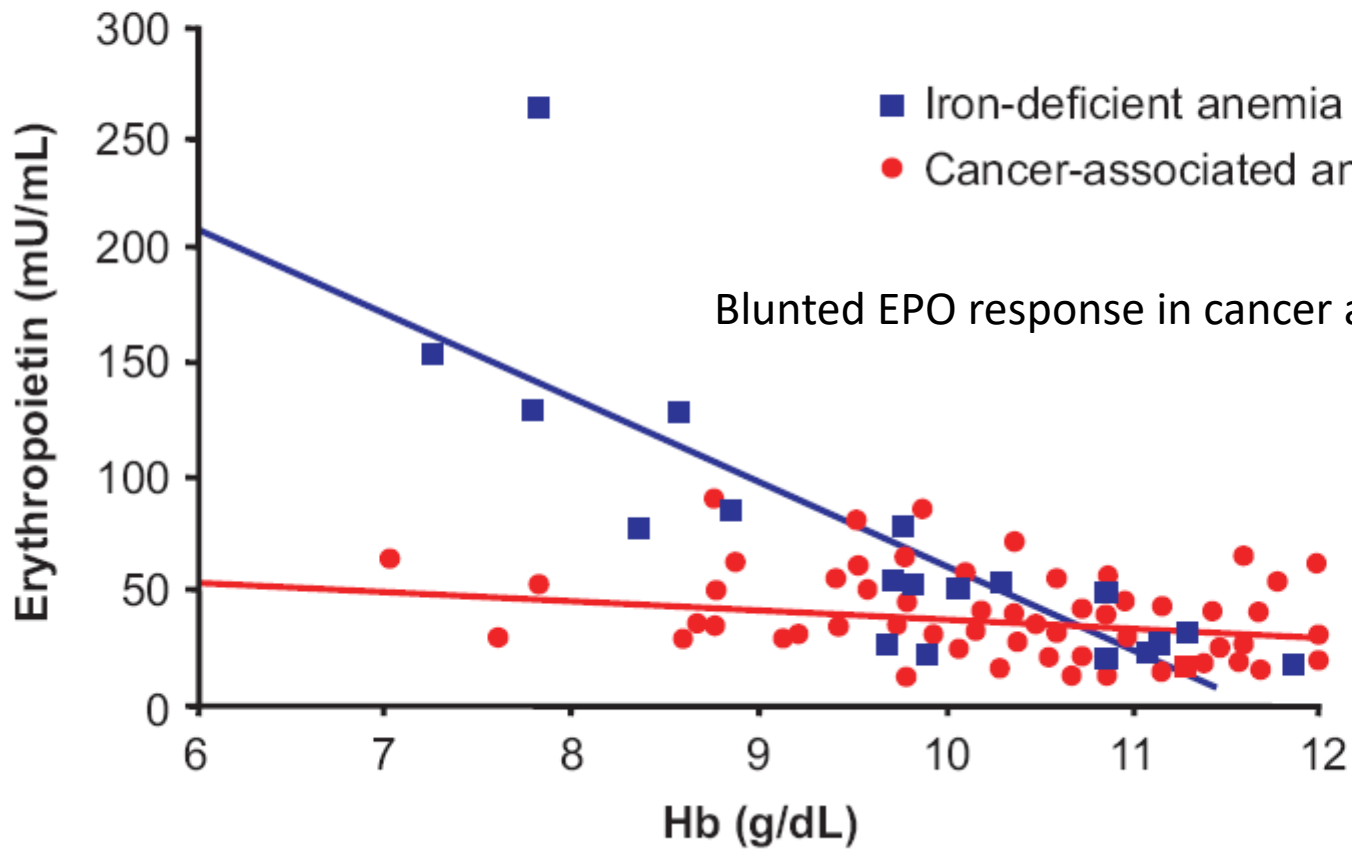
Cancer Related Anemia

- 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 Ca 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

Erythropoietin Response to Anemia



Blunted EPO response in cancer associated anemia

Miller et al. *N Engl J Med*. 1990;322:1689-1692.

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

National Comprehensive Cancer Network®

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

NCCN Guidelines Index
Table of Contents
Discussion

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	• Increased thrombotic events • Possible decreased survival • Time to tumor progression shortened	• 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	• Transfusion avoidance • Gradual improvement in anemia-related symptoms	• 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**

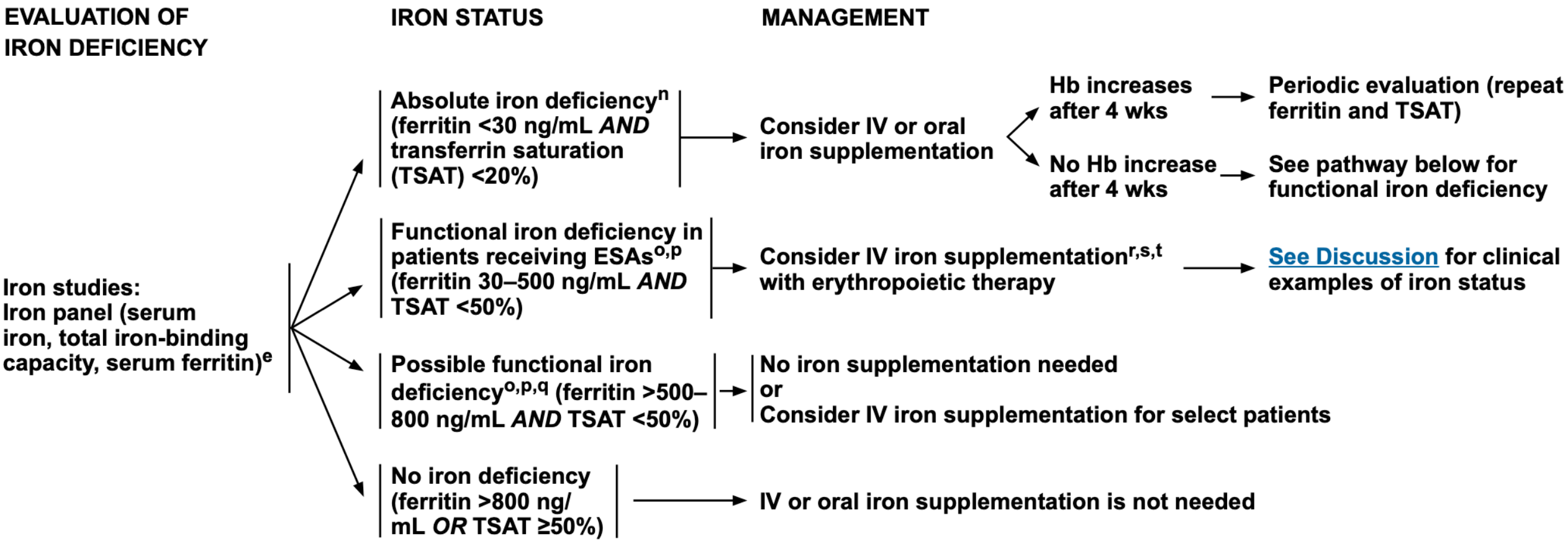
When considering RBC transfusion, see AABB Clinical Practice Guidelines: Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. Transfusion 2016;56:2627-2630.

Iron deficiency

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Management of Cancer- and Chemotherapy-Induced Anemia

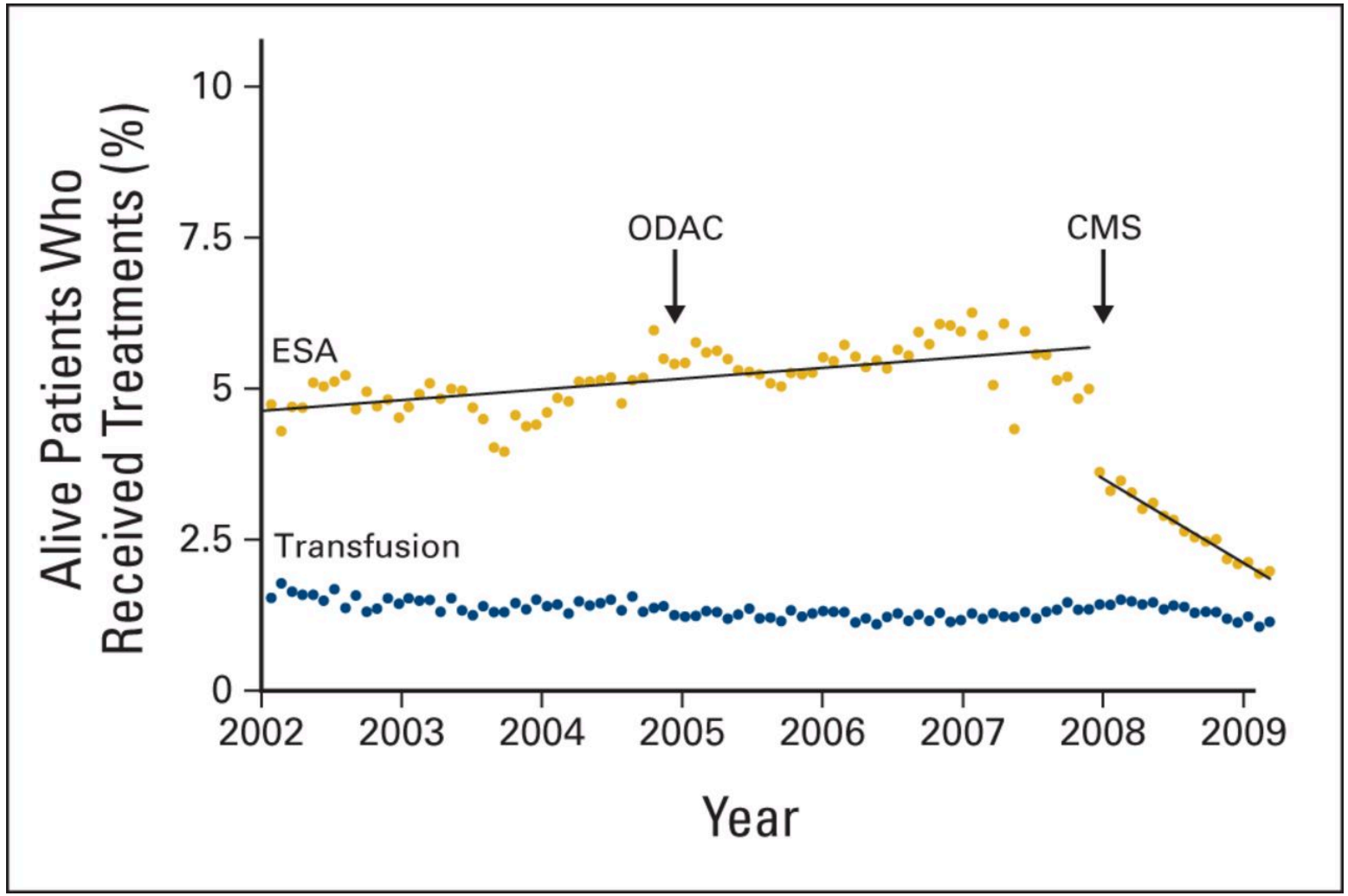
NCCN Guidelines Index
Table of Contents
Discussion



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

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



Hershman D L et al. JOP 2014;10:264-269

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 ≥ 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

From NCCN guidelines

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)

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

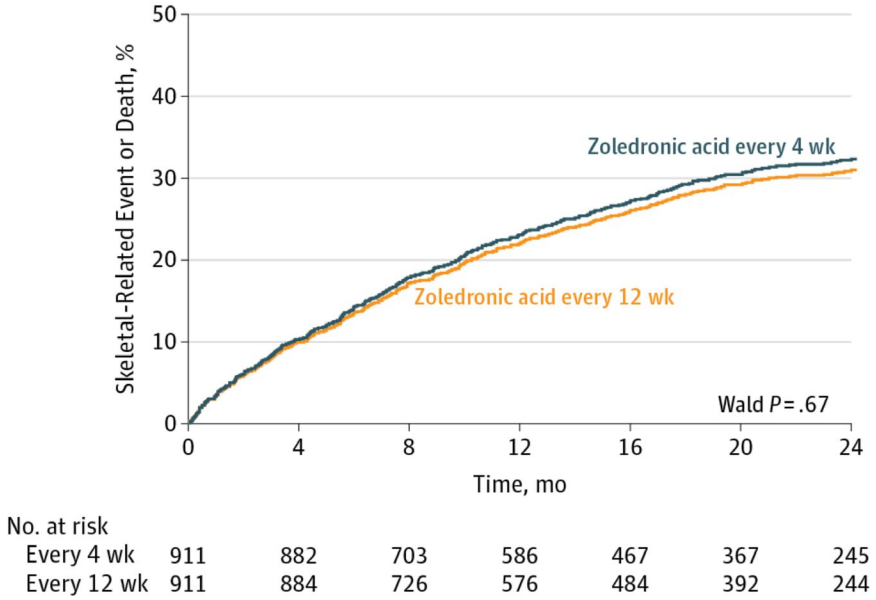
- Analogs of pyrophosphate – a major constituent of bone
- Decrease bone resorption and increase mineralization by inhibiting osteoclast activity
- Induce apoptosis in osteoclasts
- Zoledronic acid (ZA) and pamidronate are potent bisphosphonates

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 MetastasesA Randomized Clinical Trial**

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



Cause-Specific Cumulative Incidence of Skeletal-Related EventsThere 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
- 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, but downside is relatively low

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

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
- Preliminary data suggests possible beneficial effect of limb cooling
- 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

Cancer Cachexia

- Pharmacologic interventions:
- Only corticosteroids and progesterone analogs have demonstrated benefit
- Increased appetite, modest weight gain
- No effect on survival or overall QOL

Treatment of Cancer Cachexia

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

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!