Supportive Care In Oncology: Anemia, Neutropenia, Emesis, & Bone Metastases

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Disclosure

- The following individual has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation
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Objectives

- Discuss the four major classifications of chemotherapy induced nausea and vomiting (CINV)
- Review different classes of anti-emetics and develop an appropriate anti-emetic regimen based on the emetogenicity of the chemotherapy agents
- Review assessment and treatment options for adult patients with cancer and chemotherapy induced anemia (CIA)
- Evaluate risk factors for febrile neutropenia and formulate a plan for prevention and treatment
- Discuss pain management and prevention of skeletal-related events (SREs) in the setting of bone metastases

EMESIS

Types of Chemotherapy Induced Nausea & Vomiting (CINV)

1. **Acute nausea/vomiting**: occurs within **24 hours** after treatment
2. **Delayed nausea/vomiting**: occurs from **24 hours to 5 days** after treatment
3. **Anticipatory nausea/vomiting**: occurs anytime prior to the patient getting treatment (in particular if have experienced N/V in the past)
4. **Breakthrough/refractory nausea/vomiting:** occurs despite use of multiple anti-emetics; difficult to manage

✧ The occurrence of **acute nausea/ vomiting** is increased in younger women (<50 years) with low ethanol use, history of motion sickness and/or morning sickness

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Delayed CINV

- **Delayed nausea/vomiting**: occurs from **24 hours to 5 days** after treatment
- **Chemotherapy Agents Associated:**
  - Cisplatin
  - Carboplatin
  - Cyclophosphamide
  - Doxorubicin

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Key Concepts of CINV

- **Combination antiemetic therapy is generally more effective than single-agent therapy**
- **Frequency of CINV depends on each agent of the regimen**
  - Choose anti-emetic regimen based on drug with the highest emetogenic potential
- **Patient needs to be protected throughout entire risk period**
  - Lasts at least 3 days for high emetic risk agents
  - Lasts 2 days for moderate emetic risk agent
- **Algorithm defines the emetogenicity of chemotherapeutic regimens into four categories**
  - Grunberg classification
  - Updated each year by NCCN panel
  - 11 new drugs classified/re-classified in 2018 update

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Classes of Anti-Emetics

1. **5-HT3 Receptor Antagonists (5-HT3RA)**
   - ondansetron, granisetron, dolasetron
   - palonosetron
2. **NK1 Receptor Antagonists (NK1RA)**
   - fosaprepitant
   - aprepitant
3. **Steroids**
   - dexamethasone
4. **Atypical antipsychotic**
   - olanzapine
5. **Benzodiazepines**
   - lorazepam
6. **Phenothiazines**
   - prochlorperazine
   - promethazine

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5-HT3 Receptor Antagonists (5-HT3RA)

- **Ondansetron, granisetron, and dolasetron effective in preventing acute emesis**
  - Granisetron SubQ (extended release): 10 mg 30 mins prior to chemo every 7 days or every 14 days if CrCl 30-59 mL/min; Avoid if CrCl <30 mL/min
  - Granisetron Patch: 3.1 mg/24 hours applied 24-48 hours prior to chemo and can be worn for up to 7 days after chemo
- **Palonosetron**
  - Duration of action is longer compared to ondansetron (40 hours)
  - Effective in preventing acute and delayed emesis
  - Palonosetron is preferred for moderately emetogenic chemotherapy (MEC) when used with dexamethasone without a NK1RA

- **Side Effects include:** constipation and headache
  - Less side effects with palonosetron and granisetron patch
- **Increased risk for developing abnormal electrical activity (prolongation of QT interval)**

- **Clinical Pearl:** If received palonosetron, breakthrough 5-HT3s play a limited role in the delayed infusion period and management should focus on different targets

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Neurokinin-1-Receptor Antagonists (NK1RA)

- Aprepitant, fosaprepitant, and rolapitant effective in preventing delayed CINV
- Inhibit the metabolism of dexamethasone thereby increasing dexamethasone serum levels (**except:** rolapitant)
- **Clinical Pearl:** Place in therapy for prevention of CINV, not treatment; largest benefit seen in delayed CINV setting

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Dexamethasone

- Protection again CINV in both the acute and delayed setting
- Dexamethasone doses can be individualized; lower doses, change in frequency, or even elimination may be needed
  - Consider dexamethasone sparing strategies to limit SE's (such as insomnia and increase in glucose)
  - NCCN update decreased dose of dexamethasone
- **Clinical Pearl:** For patients suffering from extended delayed CINV, consider extending the course of dexamethasone. Also consider AM dosing to minimize insomnia.

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Olanzapine

- Atypical antipsychotic
- **Antagonists of multiple receptors in CINV including**: dopamine, serotonin, histamine, and acetylcholine-muscarine
- Effective in preventing acute and delayed emesis
- **2018 NCCN update:** olanzapine can be substituted for dexamethasone if patient cannot tolerate dexamethasone
- **Common SE's**: fatigue, drowsiness, and sleep disturbances
- Increased risk for developing abnormal electrical activity (prolongation of QT interval)
- **Clinical Pearl:** Consider a dose of 5-mg if the previously given 10-mg dose caused excessive sedation
  - Sedation most common on Day 2
  - Improves over time

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Benzodiazepines

- **Clinical Pearl:** Consider for anticipatory CINV or when breakthrough CINV has an anxiety component
- **Anticipatory CINV;** Consider anxiolytic therapy:
  - Lorazepam 0.5 mg IV/PO night prior to chemo and every 6 hours PRN (dose may be increased in 0.5 mg increments to 2 mg if needed)
  - Lorazepam 0.5-2 mg PO night before chemo and then repeat next day 1-2 hours prior to chemo

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Grunberg Classification

- **High emetic risk**: more than 90% of patients experience acute emesis
- **Moderate emetic risk**: more than 30-90% of patients experience acute emesis
- **Low emetic risk**: 10-30% of patients experience acute emesis
- **Minimal emetic risk**: fewer than 10% of patients experience acute emesis

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Emetogenic Classification

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTICANCER AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c]	• 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]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC <4[d] • Carmustine[d] ≤250 mg/m² • Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m²	• Dactinomycin[d] • Daunorubicin[d] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[d] <60 mg/m² • Epirubicin[d] ≤90 mg/m² • Idarubicin • Ifosfamide[d] <2 g/m² per dose • Interferon alfa ≥10 million IU/m² • Irinotecan[d]	• Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin[d] • Temozolomide • Trabectedin[d]

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Emetogenic Classification

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTICANCER AGENTS[a]

LEVEL	AGENT		
Low emetic risk (10%–30% frequency of emesis)[b]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Atezolizumab • Belinostat • Blinatumomab • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (low dose) 100–200 mg/m² • Docetaxel • Doxorubicin (liposomal) • Eribulin	• Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Interferon alfa >5 - <10 million international units/m² • Irinotecan (liposomal) • Ixabepilone • Methotrexate >50 mg/m² - <250 mg/m² • Mitomycin • Mitoxantrone • Necitumumab • Olaratumab	• Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Talimogene laherparepvec • Thiotepa • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b]	• Alemtuzumab • Avelumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine • Cytarabine <100 mg/m² • Daratumumab • Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab	• Elotuzumab • Fludarabine • Interferon alpha ≤5 million IU/m² • Ipilimumab • Methotrexate ≤50 mg/m² • Nelarabine • Nivolumab • Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pembrolizumab • Pertuzumab	• Ramucirumab • Rituximab • Rituximab and hyaluronidase human injection for SQ use • Siltuximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

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Emetogenic Classification

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

LEVEL	AGENT		
Moderate to high emetic risk[b] (≥30% frequency of emesis)	• Altretamine • Busulfan (≥4 mg/d) • Ceritinib • Crizotinib • Cyclophosphamide (≥100 mg/m^2/d) • Enasidenib • Estramustine	• Etoposide • Lenvatinib • Lomustine (single day) • Midostaurin • Mitotane • Niraparib • Olaparib	• Panobinostat • Procarbazine • Rucaparib • Temozolomide (>75 mg/m^2/d) • Trifluridine/tipiracil
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Abemaciclib • Afatinib • Alectinib • Axitinib • Bexarotene • Brigatinib • Bosutinib • Busulfan (<4 mg/d) • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide (<100 mg/m^2/d) • Dasatinib • Dabrafenib • Erlotinib • Everolimus • Fludarabine	• Gefitinib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib • Ixazomib • Lapatinib • Lenalidomide • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Neratinib • Osimertinib • Palbociclib • Pazopanib • Pomalidomide • Ponatinib	• Regorafenib • Ribociclib • Ruxolitinib • Sonidegib • Sorafenib • Sunitinib • Temozolomide (≤75 mg/m^2/d)[e] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat

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High Emetic Risk

HIGH EMETIC RISK INTRAVENOUS CHEMOTHERAPY — ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select option A, B, or C (order does not imply preference) All are category 1, start before chemotherapy:[h]	DAYS 2, 3, 4:
A • NK-1RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[k] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[l] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[l] ▸ Rolapitant 180 mg PO once[m] • 5-HT3 RA (choose one):[n,o] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once[p], 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[q]	**A** • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[q] PO/IV daily on days 2, 3, 4
B • Olanzapine 10 mg PO once[r] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[q]	**B** • Olanzapine 10 mg PO daily on days 2, 3, 4[r]

High-Emetic Risk= 3-4 drug regimen

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Moderate Emetic Risk

MODERATE EMETIC RISK INTRAVENOUS CHEMOTHERAPY — ACUTE AND DELAYED EMESIS PREVENTION[f,g,h,i,j]

DAY 1: Select option D, E, or F (order does not imply preference). All are category 1, start before chemotherapy:[h]	DAYS 2, 3:
D • 5-HT3 RA (choose one): ‣ Dolasetron 100 mg PO once ‣ Granisetron 10 mg SQ once[p] (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[q]	D • Dexamethasone 8 mg[q] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[u]: ‣ 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
E • Olanzapine 10 mg PO once[r] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[q]	E • Olanzapine 10 mg PO daily on days 2, 3[r]

- **Palonosetron is the preferred 5-HT3 RA when used in the following regimens:**
  a. In combination with olanzapine and dexamethasone
  b. In a regimen that does NOT contain an NK-1 RA

Moderate-Emetic Risk= 2-3 drug regimen

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Low and Minimal Emetic Risk

Low →

Start before chemotherapy (order does not imply preference) [g,h,v]
Repeat daily for multiday doses of chemotherapy

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

Minimal → **No routine prophylaxis →**

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Breakthrough CINV

- **General principle is to add one agent from a different class to the current regimen**
  - Olanzapine 5 mg PO daily
  - Metoclopramide 10 mg PO/IV every 4-6 hours (dose may be increased to 20 mg PO/IV every 4-6 hours if needed)
    - **Clinical Pearl:** Metoclopramide increases gut motility and may cause diarrhea therefore can be utilized to manage gastroparesis
  - Prochlorperazine 10 mg PO/IV every 6 hours
  - Promethazine 12.5 mg PO/IV every 4-6 hours (central line only)

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ANEMIA

Cancer & Chemotherapy Induced Anemia (CIA)

- **CIA is prevalent occurring in 30-90% of patients with cancer**
  - Studies have identified lung cancer and gynecologic malignancies as having increased incidence of CIA

- **Causes of anemia in patients with cancer are multifactorial & requires comprehensive evaluation**

- **If the likely cause of anemia is myelosuppresive chemotherapy, a risk assessment must be done prior to initiating treatment plan:**
  - Packed red blood cells (PRBCs)
  - Erythropoiesis-stimulating agents (ESAs) +/- iron supplementation

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Red Blood Cell Transfusion

- **Decision of offering PRBC should NOT be based on whether the Hb level has reached a certain threshold, rather NCCN outlines three general categories:**

1. **Asymptomatic without significant comorbidities**
   - Observation and periodic re-evaluation are appropriate
2. **High Risk (ie, progressive decline in Hb with recent intensive chemotherapy or radiation OR asymptomatic with comorbidities (eg, cardiac disease, chronic pulmonary disease, cerebral vascular disease)**
   - Transfusion can be considered
3. **Symptomatic**
   - Should receive transfusion

Transfusion of 1 unit of PRBCs has been estimated to result in increase in Hb level by 1 g/dL

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Erythropoietic Therapy

- **RBC production is normally controlled by erythropoietin (a cytokine produced in the kidneys)**
  - ESAs have been shown to stimulate erythropoiesis in patients with low RBC levels
- **ESAs include:**
  - Epoetin alfa
  - Darbepoetin alfa
  - Epoetin alfa-epbx (first biosimilar; FDA approved 05/18)

All considered equivalent by NCCN

- **ESAs can take weeks to elicit a Hb response, but they are effective at maintaining a target Hb level with repeated administration**

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Risks of ESA Therapy

1. **Risk for Thromboembolism (BBW)**
   - Increased thromboembolic events, including VTE
2. **Possible Increased Mortality and Tumor Progression (BBW)**
   - Studies mainly in advanced breast, cervical, head and neck, lymphoid, and non-small cell lung cancers with Hb target levels >12 g/dL
   - Delaying ESA treatment until Hb <10 g/dL results in fewer thromboembolic events and reduced mortality
3. **Risk for Hypertension/Seizures**
   - Blood pressure should be controlled prior to starting and during therapy with ESA's
4. **Risk for Pure Red Cell Aplasia (PRCA)**
   - Rare and caused by the development of neutralizing antibodies against erythropoietin
   - Predominantly occurs in those with chronic renal failure

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Hemoglobin Thresholds

- **Chemotherapy-Induced Anemia:**
  - Initiate when Hb <10 g/dL
  - Hold when Hb ≥10 g/dL

- **Chronic kidney disease (CKD)-Induced Anemia:**
  - Initiate when Hb <10 g/dL
  - Hold when Hb ≥11 g/dL (if ON dialysis)
  - Hold when Hb ≥10 g/dL (if NOT on dialysis)

- **Symptomatic Anemia in myelodysplastic syndrome (MDS):**
  - Initiate when Hb <11 g/dL or patient is symptomatic
  - Hold when Hb ≥12 g/dL

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NCCN. Myelodysplastic Syndromes. (Version 2.2019)

ESA's Recommendations

- As of 2017, the FDA no longer requires that the ESA Risk Evaluation and Mitigation Strategy (REMS) program be completed
- **Prescribers should continue to ensure that the benefits of ESA therapy outweigh its risks and keep in mind:**
  - ESA's should be discontinued once chemotherapy is complete
  - ESA's should not be used when the treatment intent is curative
  - ESA's are not recommended in patients with cancer not receiving chemotherapy, patients receiving non-myelosuppresive therapy, or those receiving myelosuppresive therapy in whom anemia can be managed by transfusion

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ESA's Dosing & Titration

	Darbepoetin Alfa
FDA approved dose	2.25 mcg/kg SC every week or 500 mcg SC every 3 weeks *See titration below
NCCN Alternative regimen	100 mcg SC every week (fixed dose) 200 mcg SC every 2 weeks (fixed dose) 300 mcg SC every 3 weeks (fixed dose) *See titration below
Titration for no response*	Increase to 4.5 mcg/kg weekly Increase up to 150-200 mcg(fixed dose) Increase up to 300 mcg (fixed dose) Increase up to 500 mcg (fixed dose)

*** No response is defined as Hb increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin, or 6 weeks of darbepoetin. Discontinue therapy after 8 weeks if no response**

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ESA's Dosing & Titration

	Epoetin Alfa
FDA approved dose (Epoetin alfa or epoetin alfa-epbx)	150 units/kg 3 times every week SC or 40,000 units every week SC *See titration below
NCCN Alternative regimen (Epoetin alfa only)	80,000 units every 2 weeks SC 120,000 units every 3 weeks SC
Titration for no response*	Increase to 300 units/kg 3 times weekly Increase to 60,000 units every week *No titration recommendations for alternative regimens

*** No response is defined as Hb increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin, or 6 weeks of darbepoetin. Discontinue therapy after 8 weeks if no response**

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Titration for No Response

- **No response** is defined as Hb increase less than 1 g/dL and remains below 10 g/dL after the initial 4 weeks of epoetin, or 6 weeks of darbepoetin
- **Discontinue therapy after 8 weeks if no response**
- **If Hb increases >1 g/dL in any 2-week period:**
  - Reduce dose by 25% for epoetin alfa or epoetin alfa-epbx
  - Reduce dose by 40% for darbepoetin alfa

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NEUTROPENIA

Chemotherapy Induced Neutropenia

- **Myeloid growth factors (MGFs)** are a class of biologic agents that regulate the proliferation, differentiation, survival, and activation of cells in the myeloid lineage
- MGFs are primarily used to decreased incidence of neutropenia
- **Neutropenia is defined as either of the following:**
  - Absolute neutrophil count (ANC) of <500 neutrophils/mcL
  - Anticipated decline to ≤500 neutrophils/mcL in next 48 hours
- **Neutropenia can progress to febrile neutropenia (FN) when:**
  - ≥38.3° orally or ≥38.0° for a duration over 1 hour
- **Risk of FN is related to the treatment regimen and delivered dose intensity**

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Risk Assessment for FN

- **Risk assessment should be done prior to first cycle of chemotherapy and includes:**
  - Disease type
  - Chemotherapy regimen (high-dose, dose-dense, or standard-dose)
  - Patient risk factors
  - Treatment intent (curative/adjuvant vs. palliative)
- **Based on the risk assessment, patient is assigned to one of the following groups:**
  - High-Risk group (>20% risk of FN)
  - Intermediate-Risk group (10%-20% risk of FN)
  - Low-Risk group (<10% risk of FN)

Most important risk factor for developing FN is age **>65 years**

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Prophylactic Use of MGFs

- NCCN and ASCO recommend **prophylactic** use of MGFs if the risk of developing FN is **>20% (HIGH-RISK)**
- NCCN recommends individualized consideration of MGF use in the **intermediate-risk** category
- For **low-risk** patients, routine use of MGFs is not recommended
  - May be considered if the patient is receiving curative/adjuvant treatment and is at a significant risk for FN
- Prophylactic use of MGFs in patients given concurrent chemotherapy and radiation is not recommended

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Regimens considered High Risk for FN

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC[b] (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Breast Cancer
- Dose-dense AC followed by T[b] (doxorubicin, cyclophosphamide, paclitaxel)[2]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[3]
- TC[a,c] (docetaxel, cyclophosphamide)[4]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[5]

Hodgkin Lymphoma
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[7]

Kidney Cancer
- Doxorubicin/gemcitabine[8]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[9]
- ICE (ifosfamide, carboplatin, etoposide)[a,10,11]
- Dose-dense CHOP-14[a,b] (cyclophosphamide, doxorubicin, vincristine, prednisone)[12,13]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[14]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[15]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[16]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[17,18]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[19]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[20] ± bortezomib (VTD-PACE)[21]

Ovarian Cancer
- Topotecan[a,22]
- Docetaxel[23]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[a,25]
- Ifosfamide/doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[29,30]
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

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Regimens considered Intermediate Risk for FN

Occult Primary- Adenocarcinoma
- Gemcitabine/docetaxel[32]

Breast Cancer
- Docetaxel[a,33,34]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only) [a,35]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[a,36]
- Paclitaxel every 21 days[a,37]

Cervical Cancer
- Cisplatin/topotecan[38-40]
- Paclitaxel/cisplatin[a,40]
- Topotecan[41]
- Irinotecan[42]

Colorectal Cancer
- FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[43]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,44]
- Epirubicin/cisplatin/5-fluorouracil[45]
- Epirubicin/cisplatin/capecitabine[45]

Non-Hodgkin's Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,46]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[47,48] including regimens with pegylated liposomal doxorubicin[49,50]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[51]
- Cisplatin/vinorelbine[52]
- Cisplatin/docetaxel[51,53]
- Cisplatin/etoposide[54]
- Carboplatin/paclitaxel [a,d,55]
- Docetaxel[53]

Ovarian Cancer
- Carboplatin/docetaxel[56]

Pancreatic Cancer
- FOLFIRINOX[e]

Prostate Cancer
- Cabazitaxel[f,57]

Small Cell Lung Cancer
- Etoposide/carboplatin[58]

Testicular Cancer
- Etoposide/cisplatin[59]

Uterine Sarcoma
- Docetaxel[60]

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MGF Options

- **Filgrastim, tbo-filgrastim, filgrastim-sndz, & filgrastim-aafi (all category 1 recommendation)**
  - Given the next day or up to 3-4 days after chemotherapy
  - **Dose:** 5 mcg/kg SubQ until post-nadir ANC recovery is normal
- **Pegfilgrastim (category 1), pegfilgrastim-jmdb, & pegfilgrastim-cbqv**
  - **Dose:** 6 mg SubQ once per cycle
  - Should be administered the day after chemotherapy
    - If needed, can administer 3-4 days after chemotherapy
    - If cannot come after, offer delivery device that is applied the same day as chemotherapy and delivers full dose of pegfilgrastim the following day
  - There should be atleast **12 days** between the dose of pegfilgrastim and the next cycle of chemotherapy
  - If regimen includes therapy on day 1 and 15, pegfilgrastim may be given 1 day after chemotherapy

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Therapeutic Use of MGFs

- Less evidence supporting the therapeutic use of MGFs for FN as an adjunct to antibiotics
- **Patients with FN who received prophylactic MGFs should continue with same agent received except:**
  - Since pegfilgrastim is long-acting, those who have received prophylactic pegfilgrastim should not be treated with MGFs
- **Patients who did not receive prophylactic MGFs, NCCN recommends risk assessment including:**
  - Age >65 years
  - Severe neutropenia (ANC <100 neutrophils/mcL)
  - Anticipated prolonged (>10 days) neutropenia
  - Documented infection (ex. Pneumonia)
  - Prior episodes of FN

If risk factors are present, MGFs should be considered

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MGF Options

- **Filgrastim, filgrastim-sndz, or sargramostim** may be administered in the therapeutic setting
  - **Filgrastim & filgrastim-sndz Dose:** 5 mcg/kg/day SubQ
  - **Sargramostim Dose:** 250 mcg/m2/day SubQ
- **Tbo-filgrastim and pegfilgrastim** have only been studied in the prophylactic setting
- Treatment should continue through post-nadir recovery

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MGF Toxicity

- **The most common toxicity is mild-moderate bone pain occurring in 10%-30% of patients**
  - Effectively controlled by non-narcotic analgesics
- **Pulmonary toxicity has been reported following the use of MGFs in patients with Hodgkin's lymphoma undergoing therapy with ABVD***
  - Increased risk of bleomycin-induced pulmonary toxicity
  - Use of MGFs is not recommended in ABVD
  - Less clear incidence in BEACOPP** but MGF support is recommended here

*doxorubicin, bleomycin,vinblastine, and dacarbazine
** bleomycin, etoposide, doxorubicin, cyclophosphamide,vincristine, procarbazine, prednisone

NCCN. Hematopoietic Growth Factors. (Version 1.2019)

BONE METASTASES

Bone Metastasis

- **Bone metastasis is a common manifestation of distant relapse from many types of solid cancers especially:**
  - Lung
  - Breast
  - Prostate
- **Goals of Management include:**
  - Pain control
  - Preserving and restoring function
  - Minimizing the risk for skeletal-related events (SREs)

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

Bone Pain

- Treatment of bone pain should always take into consideration the use of analgesic drugs

- External beam RT (EBRT), radioisotopes and targeted therapy given in conjunction with analgesics play a vital role

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

External beam RT (EBRT)

- All patients with painful bone metastasis should be offered EBRT
- **Metastatic spinal cord compression (mSCC) is an oncological emergency and requires immediate intervention:**
  - RT is the first-line treatment
  - Dexamethasone at a dose of 8-16 mg daily (tapered over 2 weeks)

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

Targeted therapy & Bone Pain

- **Radioisotopes**
  - In castrate-resistant symptomatic prostate cancer (CRPC), radium-223 is effective in reducing SREs, decreasing pain and improving survival (Category 1 recommendation)
  - Can be given in combination with denosumab or zoledronic acid
- **Bisphosphonates**
  - Zoledronic acid
  - Pamidronate
- **Denosumab**
- The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ)

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

Bisphosphonates

- In metastatic bone disease, bisphosphonates are associated with fewer SREs, fewer pathologic features, and decreased need for RT and surgery for bone pain
- **Use of bisphophonates should be accompanied by calcium and vitamin D supplementation**
  - Calcium 1200-1500 mg daily
  - Vitamin D_3 400-800 IU daily
- **Agents Used:**
  - **Pamidronate 90 mg IV over 2 hours every 3-4 weeks**
    - Use NOT recommended in extensive renal disease
  - **Zoledronic acid 4 mg IV over 15 min every 4 weeks**
    - Renally adjusted starting at a CrCl 30-60mL/min
    - **CrCl <30 mL/min:** Use is NOT recommended
- **Clinical Trials support the use of bisphosphonates for up to 2 years**

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

Denosumab

- **Use of denosumab should be accompanied by calcium and vitamin D supplementation**
  - Calcium 1200-1500 mg daily
  - Vitamin D_3 400-800 IU daily
- **Dose:** 120 mg SubQ every 4 weeks
- Denosumab is an option in the setting of significant renal disease

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.

Disease Specific Recommendations

- Zoledronic acid every 3-4 weeks or denosumab every 4 weeks is recommended for men with **CRPC** and bone metastasis to prevent or delay SREs (Category 1 recommendation)
- Bisphosphonates or denosumab should be used in **breast cancer** patients with bone metastasis, especially if in weight-bearing bone and if expected survival is 3 months or longer (Category 1 recommendation)

NCCN. Prostate Cancer. (Version 1.2019)
NCCN. Breast Cancer. (Version 1.2019)

References

1. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Antiemesis, version 2, 2017.
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3. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, version 2.2019.
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6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Multiple Myeloma, version 2.2019.
7. M.Fallon, R. Giusti et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Annals of Oncology 2018 July 24;29(4).

SUPPLEMENTAL SLIDES

Management of Iron Deficiency

- **IV iron is superior to oral iron**
- **Low-molecular-weight iron dextran, ferric gluconate, and iron sucrose are the recommended IV iron formulations**
  - Ferric carboxymaltose has not been evaluated and should only be considered when others fail
- **Recent study published in JAMA showed that the addition of parenteral iron to ESA therapy for the treatment of CIA:**
  - Improved hematopoietic response
  - Reduced the need for RBC transfusions
  - Increased Hb levels when compared to oral iron supplementation

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Parenteral Iron Preparations

	Low-Molecular-Weight Iron Dextran[15,b]	Ferric Gluconate[16,b]	Iron Sucrose[17,b]	Ferric Carboxymaltose[21,b,c,f] (in select cases)	Ferumoxytol[22,23,b,d,f] (in select cases)
Test dose[e]	Test dose required: 25 mg slow IV push	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction	Test dose at MD discretion based on risk for reaction
Dosage[14,f]	100 mg IV over 5 min[3] • Repeated dosing once weekly for 10 doses to total of 1 g or • Total dose infusion given over several hours[18,g] ▸ Calculated total iron dextran dose in 500 mL of 0.9% NaCl solution administered at 175 mL/h[19]	125 mg IV over 60 min[2,4,5,8] • Repeated dosing given once weekly for 8 doses • Individual doses above 125 mg are not recommended based on published trial results[8] • Total treatment course = 1000 mg	200 mg IV over 60 min[6] (repeated every 2–3 wks) or 200 mg IV over 2–5 min (repeated every 1–4 wks) • Individual doses over 300 mg are not recommended[20] • Total treatment course = 1000 mg	750 mg IV for patients weighing ≥50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course = 1500 mg or 15 mg/kg body weight IV for patients <50 kg (110 lbs) • Repeat dose once at least 7 days later • Total treatment course not to exceed 1500 mg	510 mg IV dose over 15 min • Repeat 510 mg dose 3–8 days later • Total treatment course = 1020 mg
Routes	IV; IM (not recommended)	IV	IV	IV	IV

Bone Pain Management

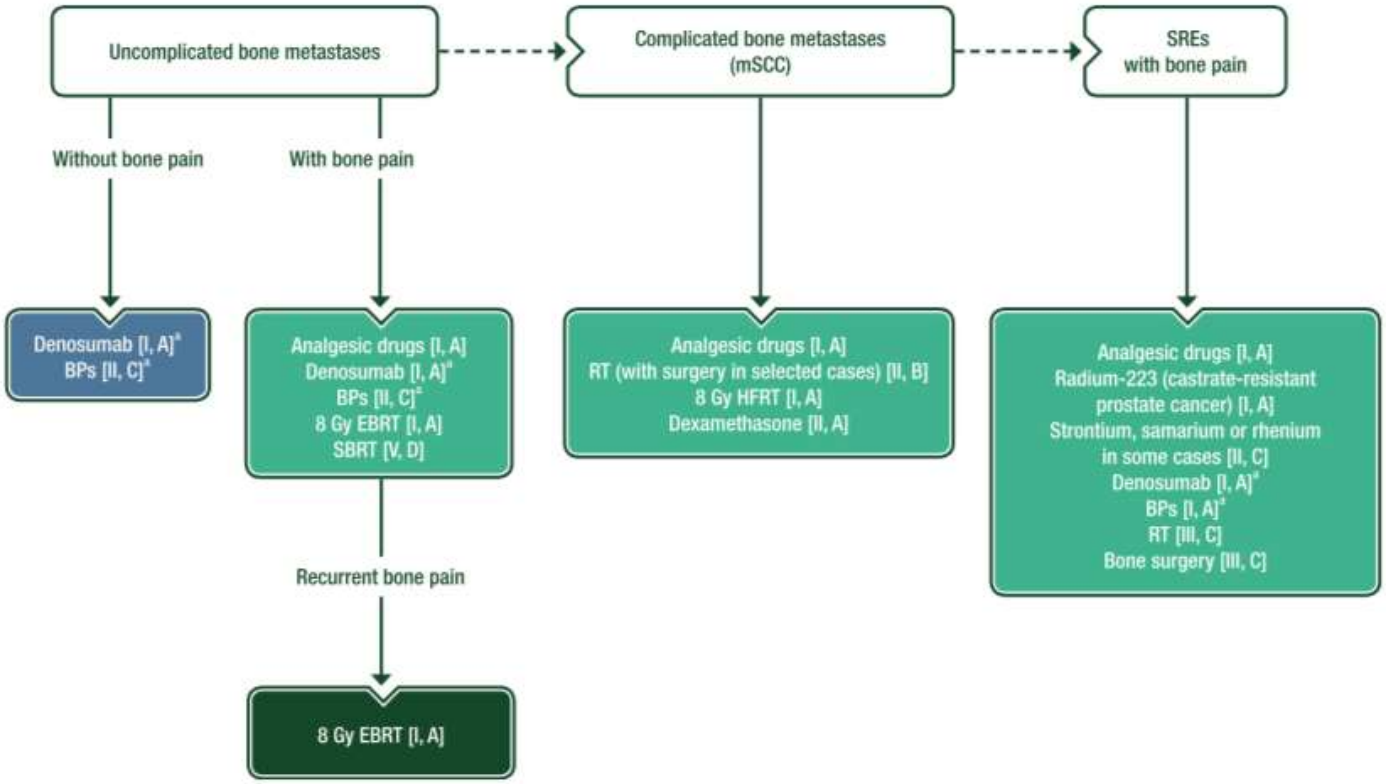

Figure 4. Treatment of pain due to bone metastases.
[a]Preventive dental measures are necessary before starting administration [III, A].
BP, biphosphonate; EBRT, external beam radiotherapy; HFRT, hypofractionated radiotherapy; mSCC, metastatic spinal cord compression; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SRE, skeletal-related event.

M.Fallon. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines 2018; 29:4.