Adverse Effects of Chemotherapy

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Classification

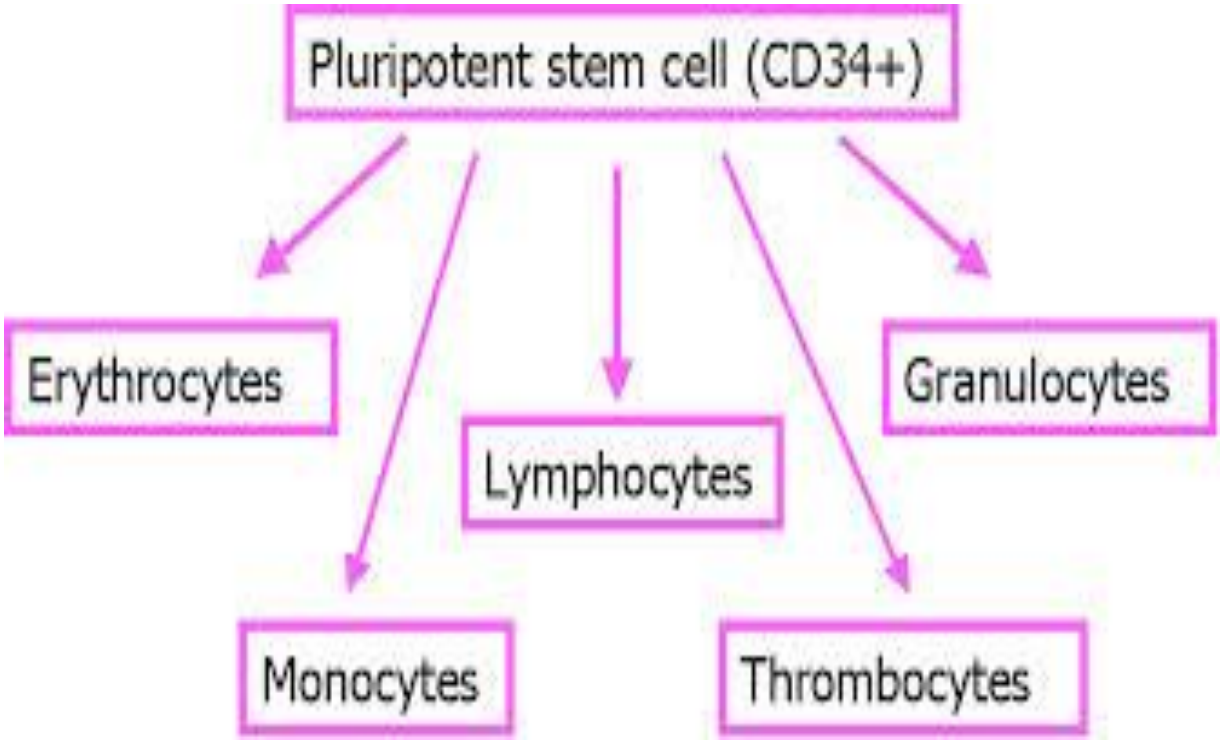
- Common and acute toxicities
- Specific organ toxicities
- Long-term complications

Common and acute toxicities

- Hematologic Toxicities
- Gastrointestinal Tract Toxicities
- Dermatologic Toxicities

Hematologic Toxicities

- This process is regulated by several cytokines



Myelosuppression

- Decreased RBCs can cause anemia (120 days)
  - Fatigue and decreased exercise tolerance.
- Having low neutrophil counts (8 hours)
  - Increases a patient's risk for bacterial infections
- Reduced platelets & thrombocytopenia (10 days)
  - Bleeding from the GI and genitourinary tracts.

Both patient-related and agent-related factors can influence the degree of cytopenia

- Agent-related factors

a) Specific agent
b) dose intensity
c) dose density

- Host factors

a) Patient age
b) Bone marrow reserve
c) The degree of myelosuppression from previous cytotoxic chemotherapy, radiation therapy, or both
d) The ability of the liver or kidney to metabolize and excrete the compounds administered.

- With most myelosuppressive agents, the patient's WBC and platelet counts begin to fall within 5 to 7 days of cytotoxic therapy administration, reach a nadir within 7 to 10 days, and recover within 14 to 26 days.

a) Dose reduction
b) CSFs
   - Filgrastim
   - Pegfilgrastim

Dosing of CSFs

- **Filgrastim**
  - 5 mcg/ kg/ day as a single daily SC injection
- **Pegfilgrastim**
  - Once per cycle as 6 mg SC in adult patients regardless of patient weight

- **Discontinue** the CSF when the neutrophil count reaches **2,000** to **4,000** cell/µL

- **Bone pain** (in sternum and pelvic region) is most commonly experienced when patients begin to recover peripheral blood cells after their nadir (Usually is relieved with **analgesic agents**)

Thrombocytopenia

- Oprelvekin
  - 50 mcg/kg/day SC until the postnadir platelet count is greater than 50,000 cells/µL or up to 21 days after chemotherapy.
  - peripheral edema, dyspnea, and pleural effusions
  - only about 20% of patients respond to oprelvekin

Anemia and erythropoietin

- Anemia usually is not a dose-limiting toxicity commonly associated with cytotoxic chemotherapy, because RBCs survive approximately 120 days.

- Chemotherapy predominantly affects RBCs by causing anisocytosis and macrocytosis
  - Folic acid analogs, hydroxyurea, purine antagonists, and pyrimidine antagonists

- Anemia commonly occurs in cancer patients secondary to the primary disease and chemotherapy

Recombinant human erythropoietin

- 150 units/ kg three times per week rounded to a standard dose of 10,000 units Or 40,000 units once weekly
- For 4 weeks
  - If the Hgb increases less than 1 g/dL, then the dose should be increased to 300 units/kg three times weekly or 60,000 units once weekly.
- patients who do not respond positively within 6 to 8 weeks should discontinue therapy.

- Increased risk for thromboembolic events.

- Hgb concentration less than 10 g/dL.
- Increased mortality in Hgb levels greater than 12 g/dL

THROMBOTIC EVENTS

- Up to one-third of apparently healthy adults who exhibit otherwise unexplained deep vein thrombosis eventually are proved to have a malignancy.

- risk factors: type of cancer, stage of cancer, comorbidities, mobility, and type of systemic anticancer therapy

- Pancreatic, stomach, kidney, lung, brain, and uterine, APL

- thalidomide, lenalidomide, and bevacizumab

GASTROINTESTINAL TRACT TOXICITIES

- The GI tract may be second only to bone marrow in its susceptibility to toxic effects produced by cytotoxic chemotherapy
  - Nausea and vomiting
  - Oral complications
  - Esophagitis
  - Lower bowel disturbances

Nausea and vomiting

- Anticancer agents or their metabolites may stimulate dopamine or serotonin receptors in the GI tract, the chemoreceptor trigger zone, or the central nervous system (CNS), which ultimately act on the vomiting center.

- Acute: few hours after the administration of the chemotherapy and can last for the first 24 hours.

- Delayed: Peak in about 2 to 3 days and can last 6 to 7 days

RISK FACTORS

- Age younger than 50 years
- Female sex
- Poor control of symptoms in prior cycles
- History of motion sickness or nausea with pregnancy, anxiety, or depression
- Shorter infusion time
- Higher dose
- More chemotherapy cycles

EMETOGENICITY OF AGENTS

- High risk agents
  - >90% of patients with symptoms
- Moderate-risk agents
  - 30% to 90% of patients with symptoms
- Low emetogenicity agents
  - Cause symptoms in 10% to 30% of patients

TREATMENT

- Combinations of antiemetics from different therapeutic classes will be more effective in most situations than a single agent.
  - 5-HT3 antagonists
  - NK1 antagonist
  - Corticosteroids

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/m^2	• Cisplatin • Cyclophosphamide >1,500 mg/m^2 • Dacarbazine • Doxorubicin ≥60 mg/m^2 • Epirubicin >90 mg/m^2 • Ifosfamide ≥2 g/m^2 per dose	• Mechlorethamine • Melphalan ≥140 mg/m^2 • Sacituzumab govitecan-hziy • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c,d]	• Aldesleukin >12–15 million IU/m^2 • Amifostine >300 mg/m^2 • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC[e] <4 • Carmustine[e] ≤250 mg/m^2 • Clofarabine • Cyclophosphamide[e] ≤1500 mg/m^2 • Cytarabine >200 mg/m^2 • Dactinomycin[e]	• Daunorubicin[e] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[e] <60 mg/m^2 • Epirubicin[e] ≤90 mg/m^2 • Fam-trastuzumab deruxtecan-nxki • Idarubicine • Ifosfamide[e] <2 g/m^2 per dose • Irinotecan[e] • Irinotecan (liposomal)	• Lurbinectedin • Melphalan <140 mg/m^2 • Methotrexate[e] ≥250 mg/m^2 • Oxaliplatin[e] • Temozolomide • Trabectedin[e]

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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 PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Low emetic risk (10%–30% frequency of emesis)[b,d,f]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/m² • Amifostine ≤300 mg/m² • Arsenic trioxide • Axicabtagene ciloleucel[g] • Belinostat • Brexucabtagene autoleucel[g] • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Copanlisib • Cytarabine (low dose) 100 mg/m² – 200 mg/m²	• Docetaxel • Doxorubicin (liposomal) • Enfortumab vedotin-ejfv • Eribulin • Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Gemtuzumab ozogamicin • Inotuzumab ozogamicin • Isatuximab-irfc • Ixabepilone • Methotrexate >50 mg/m² – <250 mg/m²	• Mitomycin • Mitomycin pyelocalyceal solution • Mitoxantrone • Mogamulizumab • Moxetumomab • Necitumumab • Olaratumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Polatuzumab vedotin	• Pralatrexate • Romidepsin • Tafasitamab-cxix • 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/m² • Daratumumab	• Daratumumab and hyaluronidase-fihj • Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab • Elotuzumab • Fludarabine • Ipilimumab • Luspatercept-aamt • Methotrexate ≤50 mg/m² • Nelarabine • Nivolumab	• Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Pembrolizumab • Pertuzumab • Pertuzumab/trastuzumab and hyaluronidase-zzxf • Ramucirumab • Rituximab • Rituximab and hyaluronidase human injection for SQ use	• Siltuximab • Temsirolimus • Trastuzumab • Trastuzumab/hyaluronidase • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

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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.

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

DAY 1: Select treatment option A[m], B[m], or C
All treatment options are category 1 and should be started before anticancer therapy[j]

DAYS 2, 3, 4:

Treatment option A (preferred), use the following combination:[n]

- Olanzapine 5–10 mg PO once[m]
- 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 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]

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 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]

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 anticancer therapy[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 anticancer therapy. ▸ 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 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]	**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 anticancer therapy[i,j,y]
Repeat daily for multiday doses of anticancer therapy

- 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

Minimal → No routine prophylaxis →

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

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Moderate to high emetic risk[b,z] (≥30% frequency of emesis)	• Altretamine • Avapritinib • Azacytidine • Binimetinib • Bosutinib >400 mg/day • Busulfan ≥4 mg/day • Capmatinib • Ceritinib	• Crizotinib • Cyclophosphamide ≥100 mg/m^2/day • Dabrafenib • Enasidenib • Encorafenib • Estramustine	• Etoposide • Fedratinib • Imatinib >400 mg/day • Lenvatinib >12 mg/day • Lomustine (single day) • Midostaurin • Mitotane	• Niraparib • Olaparib • Procarbazine • Rucaparib • Selinexor[aa] • Temozolomide >75 mg/m^2/day
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Abemaciclib • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Axitinib • Bexarotene • Brigatinib • Bosutinib ≤400 mg/day • Busulfan <4 mg/day • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide <100 mg/m^2/day • Dacomitinib • Dasatinib • Decitabine and cedazuridine	• Duvelisib • Entrectinib • Erdafitinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib ≤400 mg/day • Ixazomib • Ivosidenib • Lapatinib • Larotrectinib • Lenalidomide • Lenvatinib ≤12 mg/day	• Lorlatinib • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Neratinib • Osimertinib • Palbociclib • Panobinostat • Pazopanib • Pemigatinib • Pexidartinib • Pomalidomide • Ponatinib • Pralsetinib • Regorafenib • Ribociclib • Ripretinib • Ruxolitinib • Selpercatinib	• Sonidegib • Sorafenib • Sunitinib • Talazoparib tosylate • Tazemetostat • Temozolomide ≤75 mg/m^2/day[bb] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Trifluridine/tipiracil • Tucatinib • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat • Zanubrutinib

ORAL ANTICANCER AGENTS - EMESIS PREVENTION[i,j,cc,dd]

High to moderate emetic risk →

Start before anticancer therapy 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 Anticancer Therapy-Induced Nausea/Vomiting (AE-10)

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

Start before anticancer therapy 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 Anticancer Therapy-Induced Nausea/Vomiting (AE-10)
and
Consider changing antiemetic therapy to higher level primary therapy for the next cycle

BREAKTHROUGH TREATMENT FOR ANTICANCER THERAPY-INDUCED NAUSEA/VOMITING[j,ee]

Any nausea/ vomiting

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.

Atypical antipsychotic:[l]
- Olanzapine 5–10 mg PO daily (preferred, category 1)[ff]

• Benzodiazepine:[l]
- Lorazepam 0.5–2 mg PO/SL/IV every 6 h

• Cannabinoid:[l]
- Dronabinol capsules 5–10 mg, or dronabinol oral solution 2.1–4.2 mg/m², PO 3–4 times daily[gg]
- Nabilone 1–2 mg PO BID

• Other:
- Haloperidol 0.5–2 mg PO/IV every 4–6 h[l]
- Metoclopramide 10–20 mg PO/IV every 4–6 h[l]
- Scopolamine 1.5 mg transdermal patch 1 patch every 72 h

• Phenothiazine:[l]
- Prochlorperazine 25 mg supp PR every 12 h or 10 mg PO/IV every 6 h[l]
- Promethazine 25 mg supp PR every 6 h or 12.5–25 mg PO every 4–6 h[j]

• 5-HT3 RA:[l]
- Dolasetron 100 mg PO daily
- Granisetron 1–2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily or 3.1 mg/24-h transdermal patch every 7 days
- Ondansetron 8 mg PO every 8–12 h (16–24 mg total daily dose) or 8–16 mg IV

• Corticosteroid:[l]
- Dexamethasone 12 mg PO/IV daily

RESPONSE

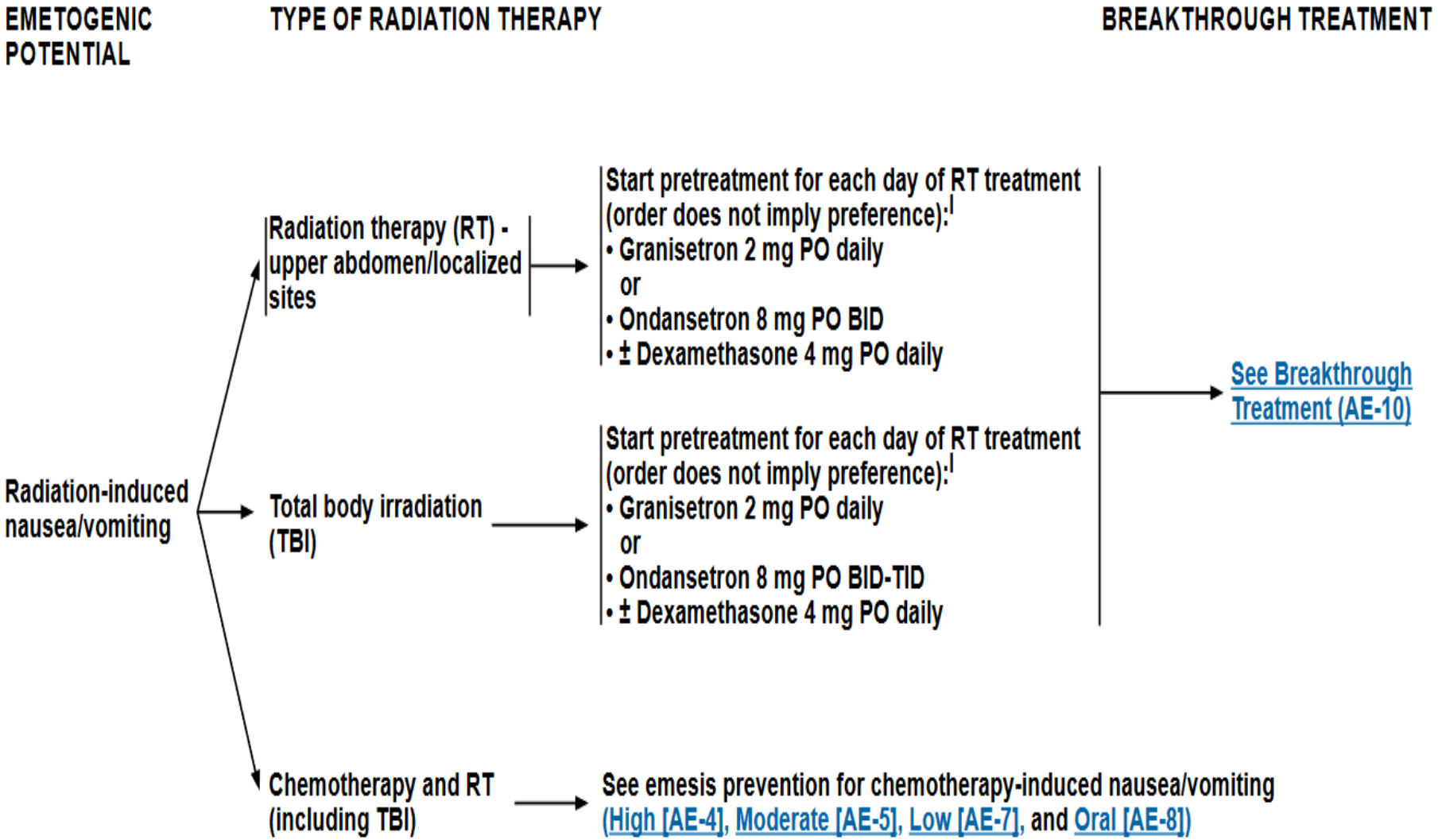
Nausea and vomiting controlled → Continue breakthrough medications, on a schedule, not PRN

Nausea and/ or vomiting uncontrolled → Re-evaluate and consider dose adjustments and/ or sequentially add one agent from a different drug class

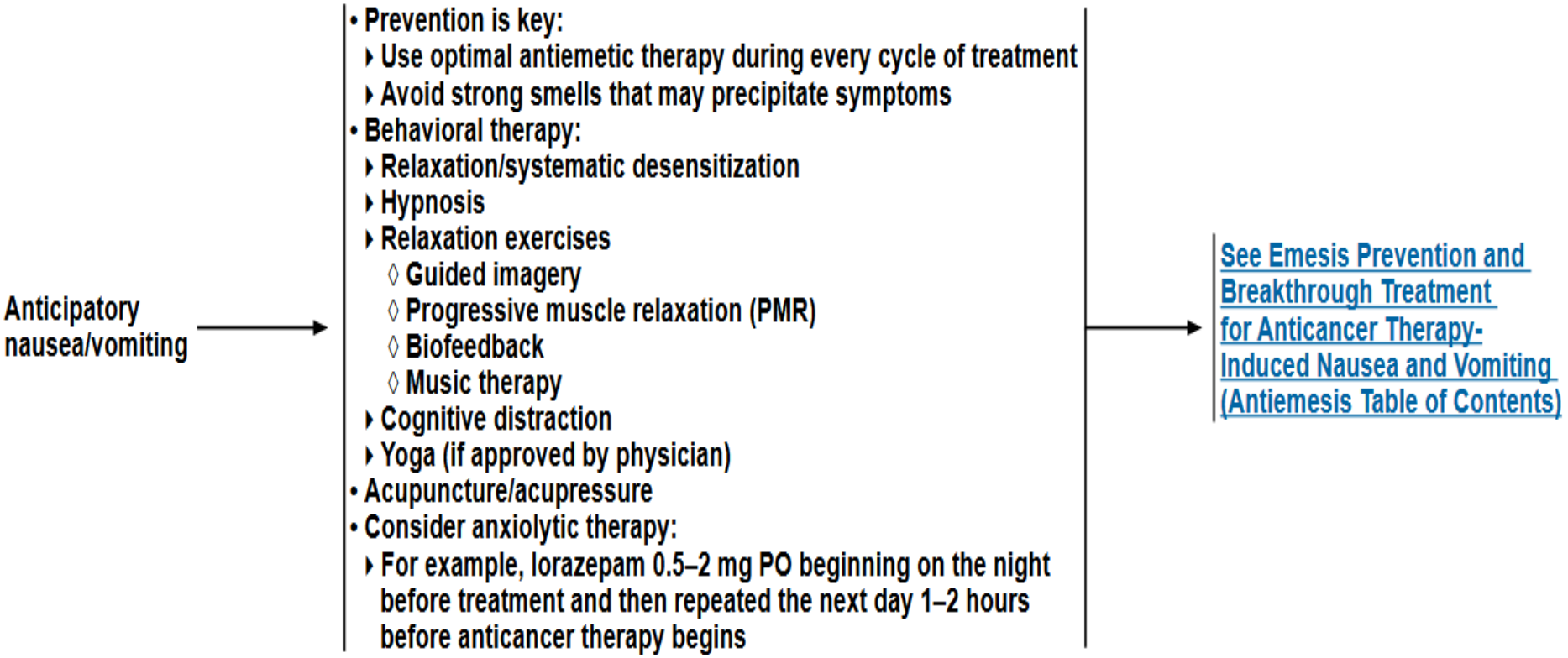
SUBSEQUENT CYCLES

Consider changing antiemetic therapy to higher level primary treatment for next cycle

RADIATION-INDUCED EMESIS PREVENTION/TREATMENT



ANTICIPATORY EMESIS PREVENTION/TREATMENT



COMPLICATIONS OF THE ORAL CAVITY

- Mucositis
- Xerostomia
- Infection
- Bleeding

- These toxicities occur because of the nonspecific effects of chemotherapy on cells undergoing rapid division, including the cells of the mouth that undergo rapid renewal with a turnover time equal to 7 to 14 days.

- Reduces the renewal rate of the basal epithelium and can cause mucosal atrophy, as well as glandular and collagen degeneration.

- Radiation therapy to the head and neck also causes mucosal atrophy by decreasing cell renewal.

- Radiation can also cause fibrosis of the salivary glands, muscles, ligaments, and blood vessels, and damage to the taste buds.

- The combined effects of chemotherapy and radiation therapy on the oral mucosa can also cause infection and bleeding in the oral cavity.

- Because the oral mucosa is highly vascular and frequently traumatized, bleeding occurs commonly with thrombocytopenia.

- cytotoxic chemotherapy and neutropenia can alter the extensive microbial flora harbored in the oral cavity, thus leading to oral infections.

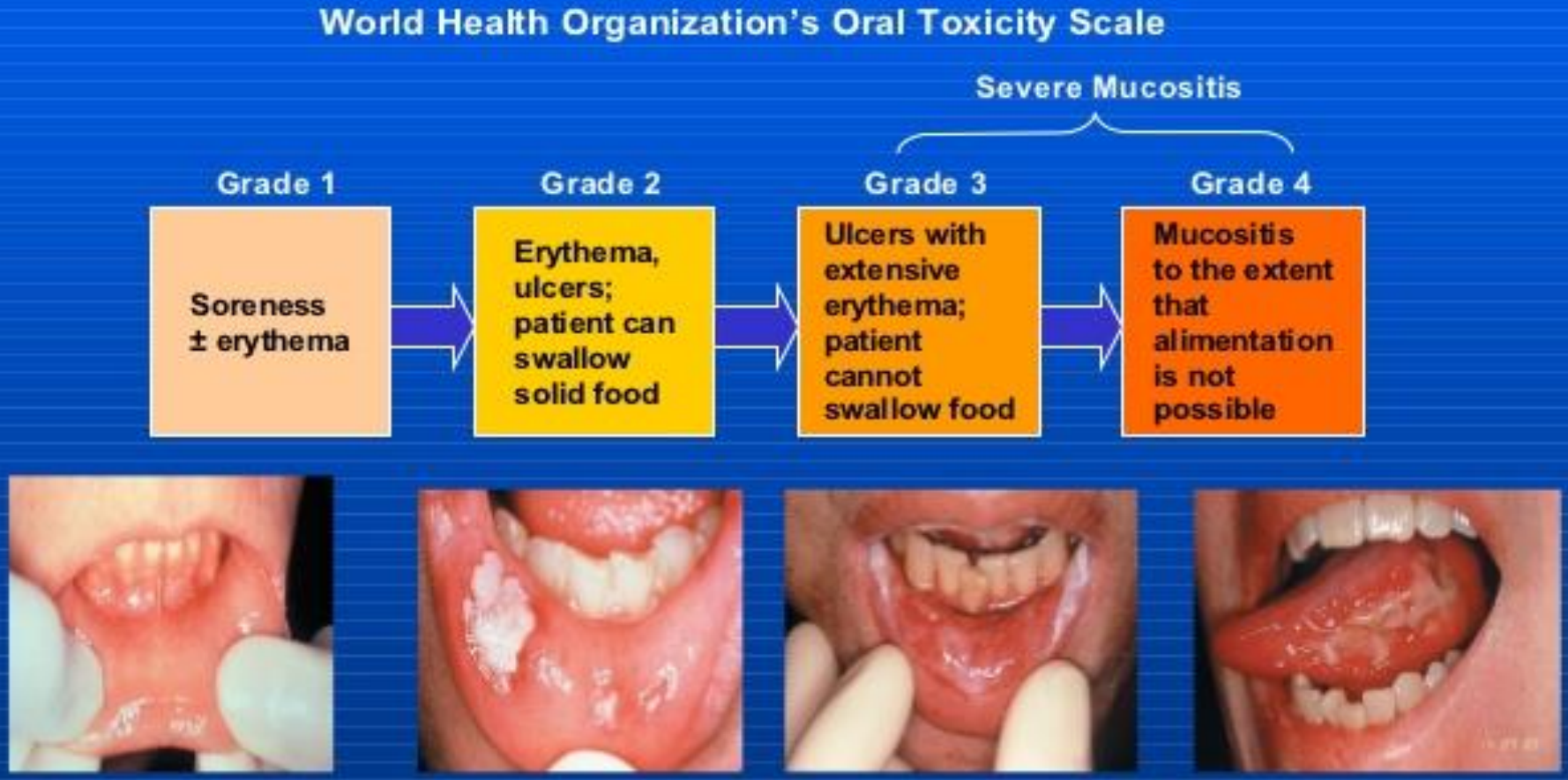
MUCOSITIS

- Signs and symptoms generally occur about 5 to 7 days after chemotherapy or at almost any point during radiation therapy.

- Lesions generally regress and resolve completely in approximately 1 to 3 weeks, depending on their severity

1) **methotrexate**
2) **fluorouracil**
3) **cytarabine**
4) **doxorubicin**
5) **etoposide**
6) **melphalan**
7) **bleomycin**

WHO's Oral Toxicity Scale

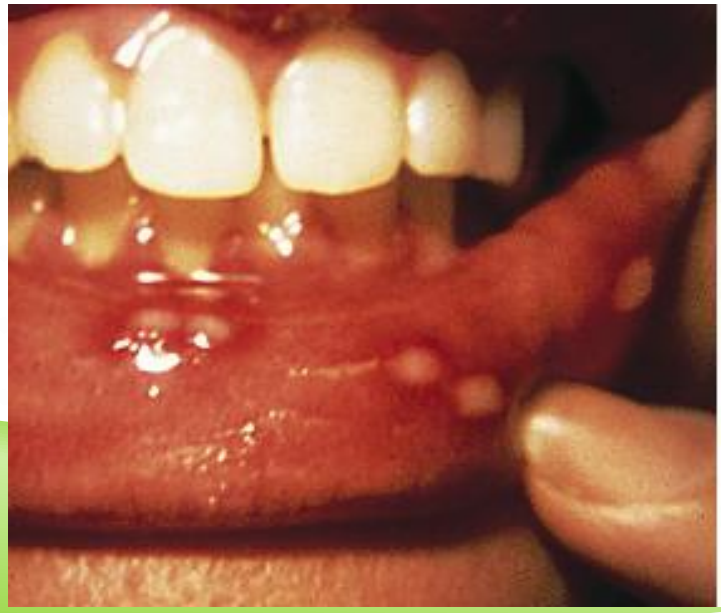


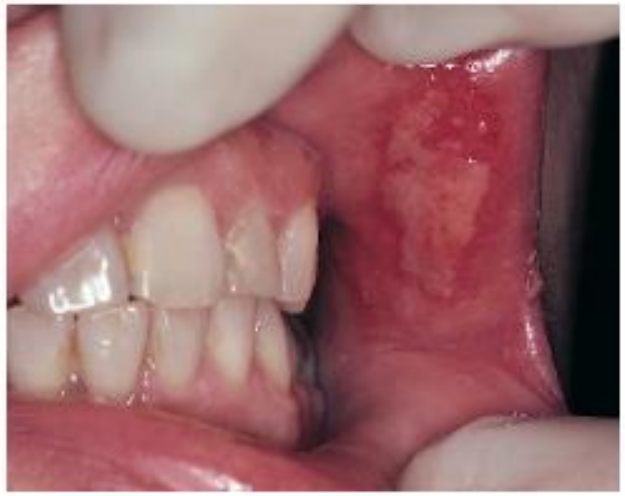
TREATMENT

- Topical anesthetics
  - Equal portions of lidocaine, diphenhydramine, and magnesium-containing or aluminum-containing antacids
- Sucralfate
- Gelclair
  - A bio-adherent oral gel containing polyvinylpyrrolidone, hyaluronic acid, and glycyrrhetinic acid

PREVENTION

- Ice chips
- Chlorhexidine gluconate 0.12%
- Palifermin (a keratinocyte growth factor)





XEROSTOMIA (DRY MOUTH)

- One of the most frequent side effects of radiation therapy to the head and neck
  - Loss of salivary buffering capacity
  - Lower salivary pH
  - Decreased salivary immunoglobulin A
  - Reduction of saliva production
  - Alter the sense of taste
  - Causes dental caries

MANAGEMENT

- Pilocarpine
- Saliva substitutes
- Sugar free gum or hard candy
- Ice chip
- Amifostine
  - An organic thiophosphate chemoprotectant agent,

LOWER GASTROINTESTINAL TRACT COMPLICATIONS

- Malabsorption
  - Villus atrophy and cessation of mitosis within GI crypts
  - Swelling and dilation of mitochondria and endoplasmic reticulum and shortening of the microvilli.
- Diarrhea
  - Irinotecan, high-dose cytarabine, or fluorouracil.
- Constipation
  - Vinca alkaloids, thalidomide.

DIARRHEA

- Irinotecan
  - Early-onset and late-onset diarrhea
  - Atropine IV or SC 0.25 to 1 mg for early onset
  - Loperamide 4 mg with the first episode of diarrhea and repeat doses of 2 mg every 2 hours until 12 hours have passed without a bowel movement

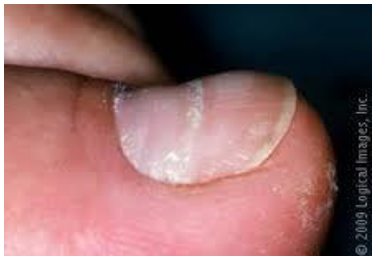
Dermatologic toxicities

- Alopecia
- Hyperpigmentation
- Radiation recall
- Photosensitivity
- Nail changes
- Hand-foot syndrome
- Acneiform rashes
- Hypersensitivity reactions
- Extravasations

Alopecia

- Because hair bulb cells replicate every 12 to 24 hours, the cells are susceptible to cytotoxic agents
- Thinned or weakened hair shaft or failure to form hair
- Begins 7 to 10 days after one treatment, with prominent hair loss noted within 1 or 2 months.
- Regeneration 1 to 2 months after therapy completion
- The color and texture of hair may be altered; the new hair may be lighter, darker, or curlier as it regrows.
- Cyclophosphamaide, antracyclines, melphalan, etoposide

NAIL CHANGES



- The growth of fingernails and toenails is arrested in a manner similar to hair growth.

- Within weeks, these pale horizontal lines (“Beau’s lines”) begin to appear in the nail beds (in patients receiving chemotherapy for more than 6 months).

- normally disappear from the fingernails in approximately 6 months.

- 40% with paclitaxel and docetaxel
- cyclophosphamide, fluorouracil, daunorubicin, doxorubicin, bleomycin are less well understood.

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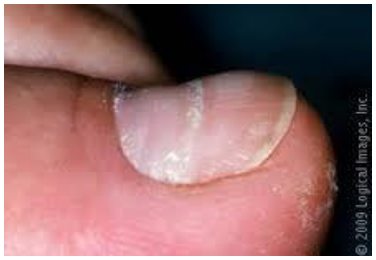

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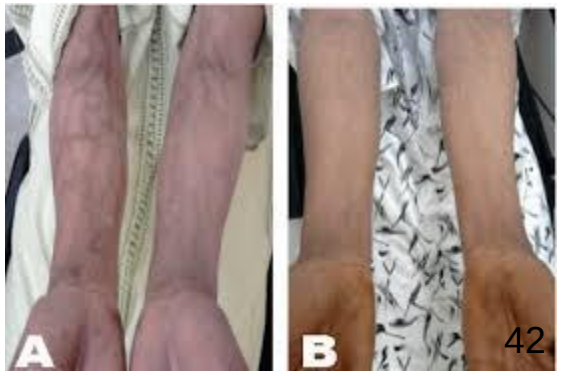
DERMATOLOGIC PIGMENT CHANGES

- hyperpigmentation> hypopigmentation
- widespread cutaneous hyperpigmentation: Busulfan, cyclophosphamide, fluorouracil, dactinomycin, and hydroxyurea
- Methotrexate can cause hyperpigmented banding of light-colored hair, “flag sign”of chemotherapy.
- peculiar serpiginous hyperpigmentation (5fu and bleomycin)



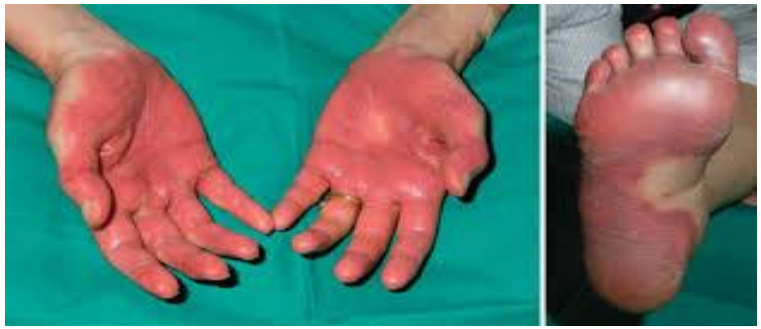
Hand-foot syndrome

acral erythema or the palmar-plantar erythrodysesthesia

- Tender, erythematous skin on the palms of hands and sometimes on the soles of feet, Tingling, burning, or shooting sensations in their hands or feet

- Cytarabine, fluorouracil, doxorubicin, liposomal doxorubicin, methotrexate, capecitabine, and hydroxyurea, sunitinib and sorafenib

- Discontinuation of the medication will help to resolve the reaction

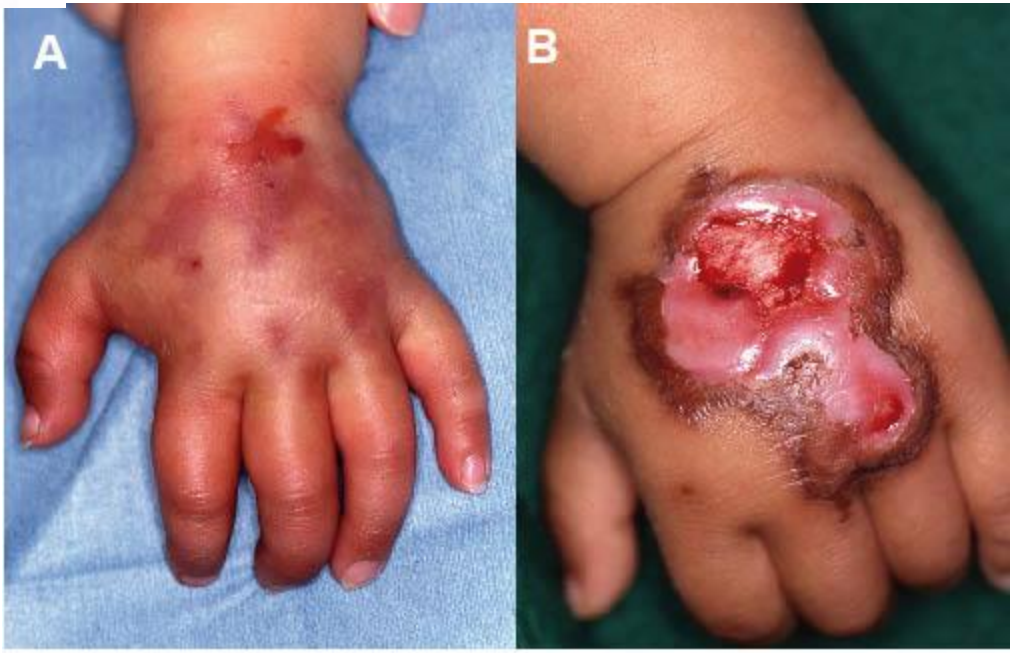


Irritant and vesicant reactions

- Transient local irritation
- Irritation of the vein
- Extravasation
- Agents known to bind to DNA (i.e., the anthracyclines) have the propensity to produce the most severe damage

Management

- Stopping the injection
- Cold compresses to the extravasation site and elevation of the extremity
- Warm compresses
  - Vinca alkaloids, Epipodophyllotoxins
- Specific antidotes
  - Dexrazoxane
  - Hyaluronidase


A
B

SPECIFIC ORGAN TOXICITIES

Neurotoxicity

- Methotrexate
  - High-dose IV methotrexate causes acute encephalopathy
  - Is usually transient and reversible
  - menangitis
- High doses of cytarabine
  - Encephalopathy
  - Cerebellar dysfunction
  - menangitis
  - Leukoencephalopathy
- Asparaginase and PEG-aspargase
  - Encephalopathy
  - Stupor, coma, excessive somnolence, disorientation, hallucination, or severe depression

Peripheral neuropathy

- Vincristine, Vinblastine & Vinorelbine
- cisplatin & Oxaliplatin
- Etoposide
- Paclitaxel & Docetaxel
- Bortezomib
- Thalidomide & Lenalidomide

- Unlike the vinca alkaloids, most of these agents cause numbness only and not a loss of reflexes, or weakness.

- Patients may report sensory loss and pain, incidence may be related to **cumulative doses** as well as **individual risk factors** such as history of diabetic neuropathy.

Peripheral neuropathy

- Vincristine and vinblastine
- Paresthesia (numbness and tingling) involving the feet and hands (within the first days to weeks of therapy.)

- peripheral nerve toxicity commonly is bilateral and symmetric and is often referred to as a “stocking-glove” neuropathy.

  - Pain and temperature sensory loss
  - Depression of deep tendon reflexes
  - Motor weakness with a foot drop or muscle atrophy

- These complications are either partially or completely reversible, but recovery often takes several months.

Oxaliplatin

- Oxaliplatin-induced neurotoxicity manifests as an acute neurosensory complex as well as a cumulative sensory neuropathy.
- Hyper excitability of peripheral nerves causes an 85% to 95% incidence of paresthesia and dysesthesias of the hands, feet, and the perioral region.
- These effects are precipitated by exposure to cold.
- Calcium and magnesium infusions

Cranial nerve toxicity

- Vinca alkaloids
  - Ptosis or ophthalmoplegia
  - Trigeminal neuralgia, facial palsy, and vocal cord paralysis
  - Jaw pain
- Cisplatin
  - Ototoxicity
  - direct toxic effect on the cochlea

Autonomic neuropathy

- Vincristine & vinblastine
  - Colicky abdominal pain with or without constipation
    - Prophylactic laxatives
    - Senna derivatives or bisacodyl and stool softeners also may be used concurrently
  - Bladder atony with urinary retention
  - Impotence
  - Orthostatic hypotension

Cardiotoxicity

- **Cardiomyopathy:**
  - Anthracycline
  - Formation of reactive oxygen species
- **Risk factors:**
  - Total cumulative dose
  - Mediastinal radiation therapy
  - Pre-existing cardiac disease
  - Hypertension
  - Concurrent chemotherapy agents
- **Prevention:**
  - Low doses administered weekly or prolonged continuous IV infusions
  - Dexrazoxane is a chemoprotectant that reduces the incidence and severity of cardiomyopathy

Trastuzumab

  - Dyspnea, increased cough, peripheral edema, and reduced ejection fraction
  - direct and not dependent on cumulative dose or treatment duration
- **Arrhythmias**
  - Doxorubicin
  - Paclitaxel
  - Dasatinib, nilotinib, lapatinib, pazopanib, and sunitinib
- **Hypertension**
  - Bevacizumab,sunitinib, sorafenib, and pazopanib

Nephrotoxicity

- Cisplatin, a platinum heavy-metal complex
  - Dose limiting toxicity
  - Acute renal failure
  - Tubular dysfunction and decreased GFR
    - Proximal tubular dysfunction causes urinary excretion of protein and magnesium as well as decreased reabsorption of salt and water
    - Hypomagnesemia, hypocalcemia, hyponatremia, and hypokalemia
  - Chronic renal failure

Prevention

- Hydration with saline
  - 2 to 3 L of normal saline during 8 to 12 hours to maintain a urine output of 100 to 200 mL/hr for at least 6 hours after treatment
- Prophylactic magnesium
  - 16 mEq IV daily during a 5-day course of cisplatin followed by 60 mEq orally (20 mEq three times daily) between courses
- Amifostine
  - scavenges the free radicals
  - 910 mg/m^2 , once daily as a 15-minute IV infusion, 30 minutes before chemotherapy
  - Can cause significant hypotension
- Dose reduction in decreased GFR

Proteinuria

- **Bevacizumab**, an anti-VEGP monoclonal antibody
  - Inhibition of nitric oxide synthesis
  - Lead to an increase in peripheral resistance and endothelial dysfunction
  - Glomerular injury lead to glomerulonephritis

Acute Tubular Obstruction

- **Methotrexate**
  - Tubular precipitation (poorly soluble at a pH less than 7)
  - Hydration and brisk diuresis to produce urine output of 100 to 200 mL/hour for at least 24 hours after administration.
  - A urine pH greater than 7.0 by administration of 25 to 50 mEq/L sodium bicarbonate within the hydration fluid.

Hemorrhagic Cystitis

- Ifosfamide
  - Acrolein is responsible for urotoxicity causing a direct irritation of the bladder mucosa
  - Painful urination, frequency, and hematuria.
  - Mesna for prevention
  - 20% of the ifosfamide dose given at zero, 4, and 8 hours after ifosfamide (for a total mesna dose of 60% of the ifosfamide dose).
  - Repeated administration is required because mesna has a much shorter elimination halflife (<1 hour) than ifosfamide.

Pulmonary Toxicities

- Bleomycin
  - The highest incidence of pulmonary toxicity
  - Interstitial pneumonitis followed by pulmonary fibrosis
    - nonproductive cough and dyspnea
  - The most significant factor is the cumulative dose
  - Mortality is about 50%
- Chlorambucil and cyclophosphamide

Hepatotoxicity

- Interfering with the mitochondrial function of the hepatocyte
- Depleting hepatic glutathione stores
- Decreasing bile flow
- Causing phlebitis of the central hepatic vein to produce veno-occlusive disease

- Asparaginase
- Carmustine
- Cytarabine
- Mercaptopurine
- Methotrexate
- Irinotecan
- Oxaliplatin

Long-Term Complications of Anticancer Therapy

Second malignancies

- Acute myeloid leukemia
  - Etoposide and anthracyclines
    - Occur 1 to 3 years after the completion of chemotherapy
  - Melphalan
    - 5 to 7 years after chemotherapy

- Risk factors
  - Large doses
  - Continuous daily dosing
  - Prolonged treatment periods
  - Age older than 40 years
  - Concomitant radiation therapy

Fertility and Teratogenicity

- Cyclophosphamide
  - infertility in men and women and gonadal failure
- Procarbazine
  - Azoospermia