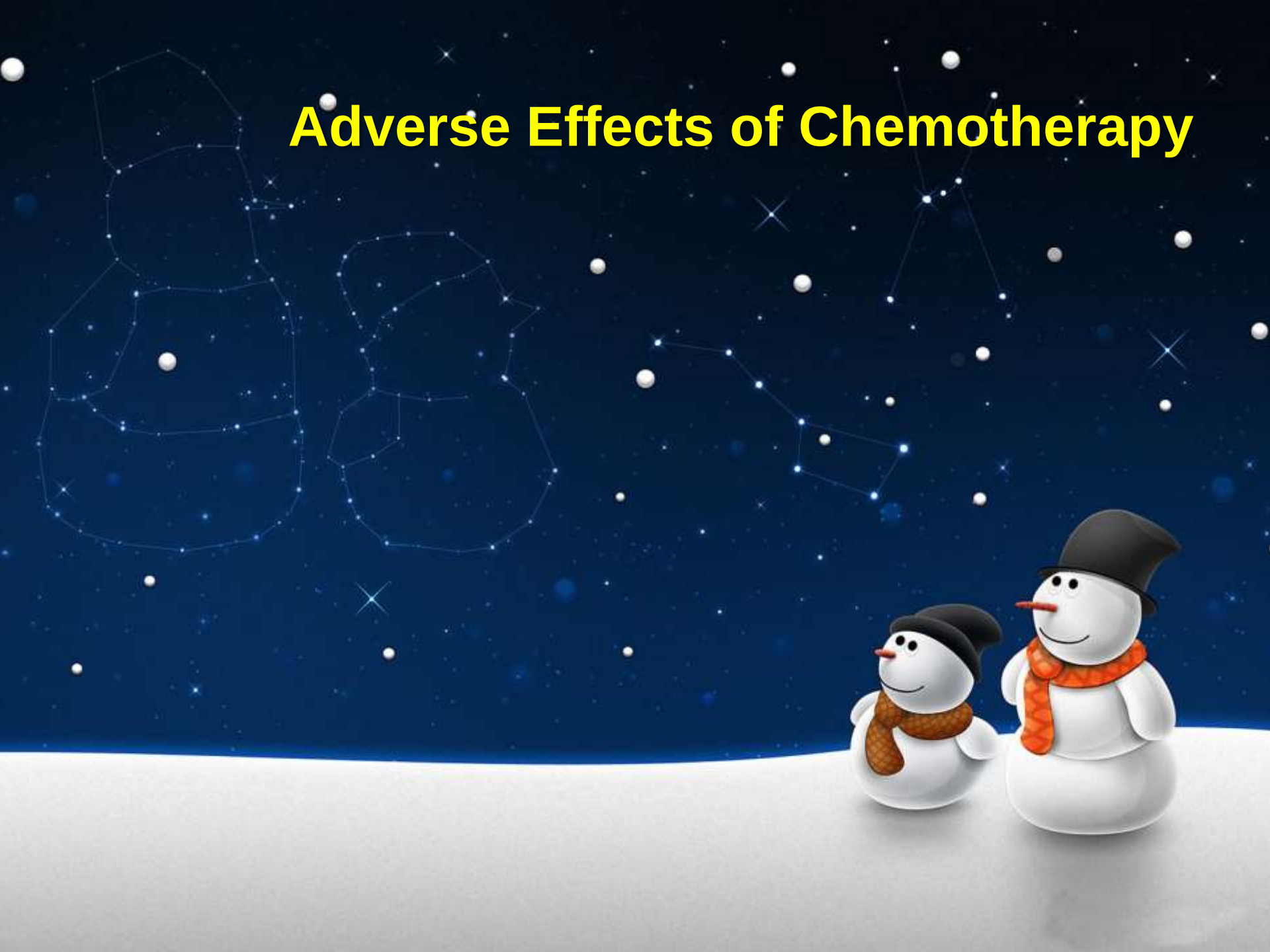
Adverse Effects of Chemotherapy



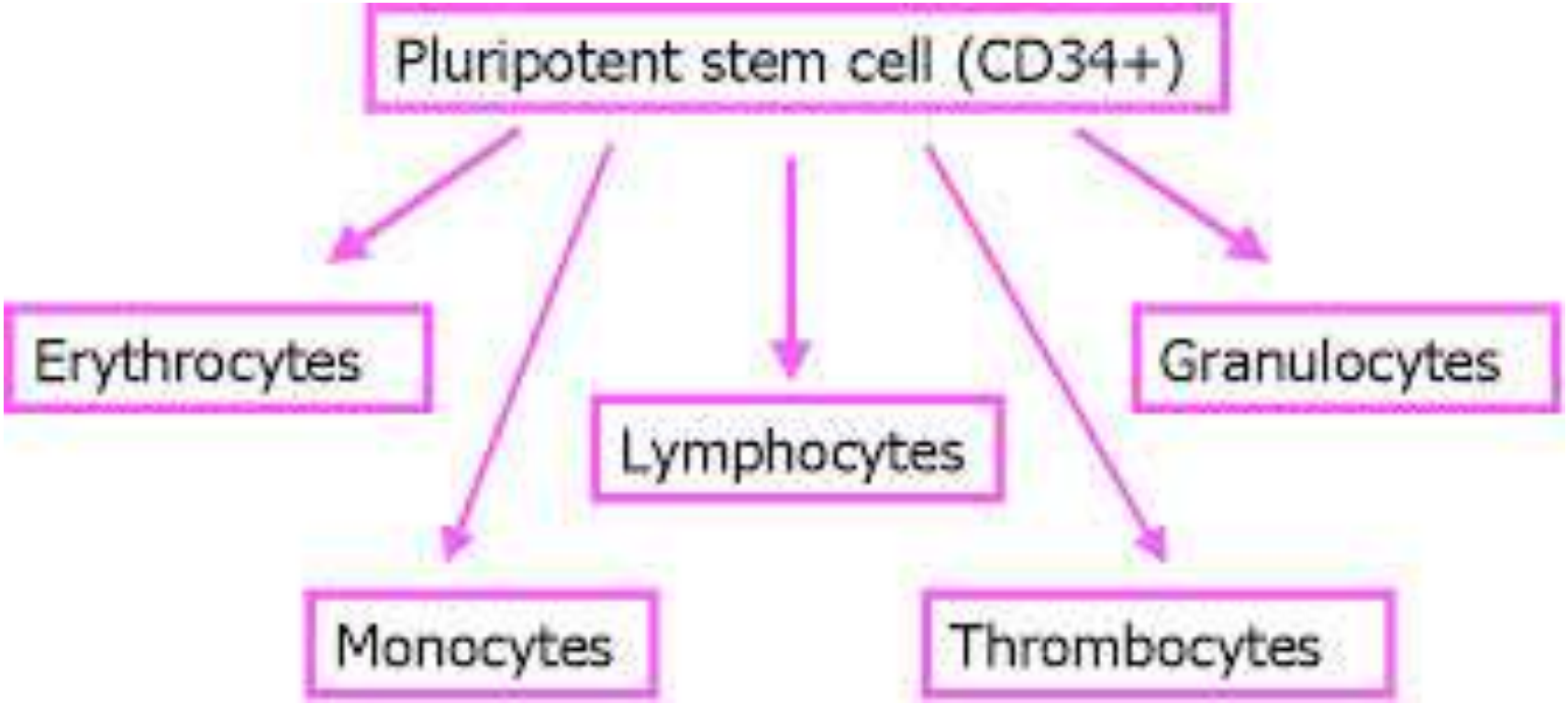
Introduction

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

COMMON AND ACUTE TOXICITIES

- Hematologic Toxicities
- Gastrointestinal Tract Toxicities
- Dermatologic Toxicities

Hematologic Toxicities



Myelosuppression

- Decreased RBCs can cause anemia
  - fatigue and decreased exercise tolerance.
- Having low neutrophil counts
  - increases a patient's risk for bacterial infections
- Reduced platelets & thrombocytopenia
  - bleeding from the GI and genitourinary tracts.

Factors influence the degree of cytopenia

- Agent-related factors
  - Specific agent
  - Dose intensity
  - Dose density
- Host factors
  - Patient age
  - Bone marrow reserve
  - Previous cytotoxic chemotherapy
  - Liver or kidney function

Neutropenia

- 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.

Prevention

- Dose reduction
- CSFs
  - Filgrastim
  - Pegfilgrastim

ASCO recommendation

- Primary prophylaxis:
  - For all patients receiving chemotherapy regimens that have been previously reported to cause an incidence of approximately 20% febrile neutropenia

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 is most commonly experienced when patients begin to recover peripheral blood cells
- Usually is relieved with analgesic agents

Treatment

- The ASCO guidelines currently do not support routine use of CSFs in patients with febrile neutropenia, except:
  - Age >65 years
  - Pneumonia
  - Fungal infection
  - Hypotension
  - Sepsis syndrome

Thrombocytopenia

- Most commonly, thrombocytopenia is managed via the use of platelet transfusions and modifications to the chemotherapy dosing scheme
- Oprelvekin
- Romiplostim

Anemia and erythropoietin

- 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

- ESAs are recommended for anemic patients with cancer who are receiving myelosuppressive chemotherapy and the intent of treatment is not curative, with the possible exception of small cell lung cancer as there are no clinical trials reporting a deleterious impact on survival

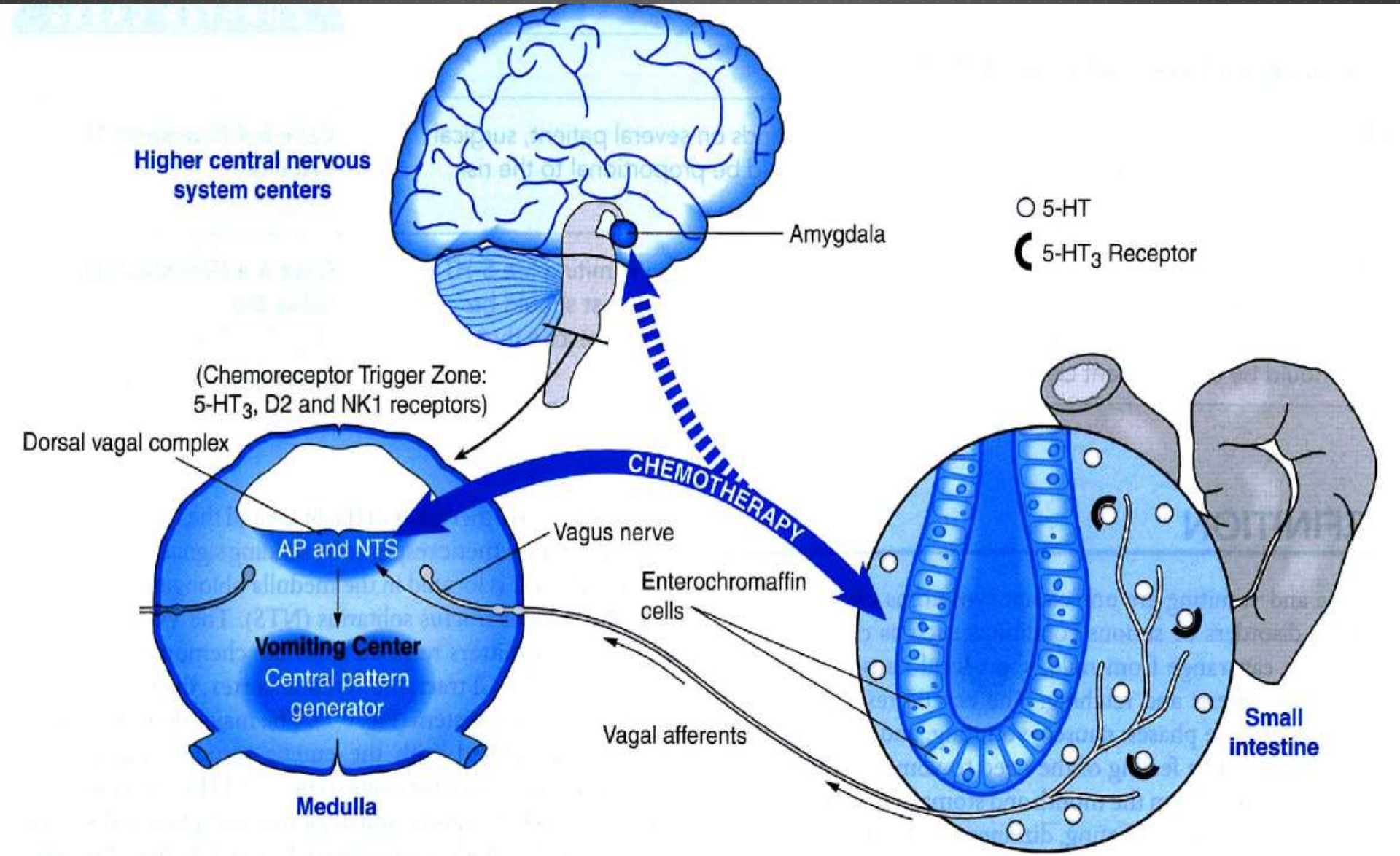
- As recommended by the FDA, treatment with an ESA should not be initiated until the Hgb is less than 10 g/dL and there is an additional 2 months of chemotherapy planned

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.
- Emesis most commonly occurs on the first day of chemotherapy and often persists for several days thereafter.


Higher central nervous system centers
Amygdala
5-HT
5-HT3 Receptor
(Chemoreceptor Trigger Zone: 5-HT3, D2 and NK1 receptors)
Dorsal vagal complex
CHEMOTHERAPY
Vagus nerve
AP and NTS
Enterochromaffin cells
Vomiting Center
Central pattern generator
Vagal afferents
Small intestine
Medulla

- Acute phase
  - Symptoms occur within a few hours after the administration of the chemotherapy and can last for the first 24 hours.
- Delayed phase
  - 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.

5-HT3 ANTAGONISTS

- Inhibit the action of serotonin in the GI tract and the CNS and thereby block the transmission of emetic signals to the VC.
- One component of optimal antiemetic prophylaxis for acute CINV
- Ondansetron, Granisetron, Dolasetron, and Palonosetron.
- All of the 5-HT3 antagonists are considered to have equivalent efficacy with response rates of 60% to 80%

CORTICOSTEROIDS

- May decrease serotonin release, antagonize 5-HT3, or activate corticosteroid receptors in the medulla of the CNS.
- Dexamethasone improves the antiemetic control of 5-HT3 antagonists by about 15% to 20%
- In addition to its use in the acute phase of CINV, dexamethasone is one of the cornerstone agents used to prevent delayed CINV

NEUROKININ 1 RECEPTOR ANTAGONISTS

- Aprepitant, is active in both the acute and delayed phases
- Aprepitant is metabolized by the CYP3A4 enzyme system
- Dexamethasone dose should be reduced by about one-half of the usual dose when these drugs are used together.
- Enhance warfarin metabolism

OLANZAPIN

- Antagonizes several serotonin and dopamine receptors as well as other neurotransmitter receptors.
- Olanzapine has activity both in the prevention of CINV in patients at high and moderate risk and in rescue treatment for patients with refractory nausea and vomiting

Medication	Indication	Dose
Aprepitant	Acute and delayed	po: 125mg on day 1, 80 mg on days 2 and 3
Dexamethasone	Acute High emetogenicity Moderate emetogenicity low emetogenicity Delayed	PO/IV: 12mg (with aprepitant) or 20 mg (without aprepitant) PO/IV:8-12 mg PO/IV:4-8 mg PO/IV:8 mg daily days 2-4 or or PO: 4 mg BID days 2-4
Granisetron	Acute	IV: 1 mg or 0.01 mg/kg PO: 2 mg

COMPLICATIONS OF THE ORAL CAVITY

- Mucositis
- Xerostomia
- Infection
- Bleeding

MUCOSITIS

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

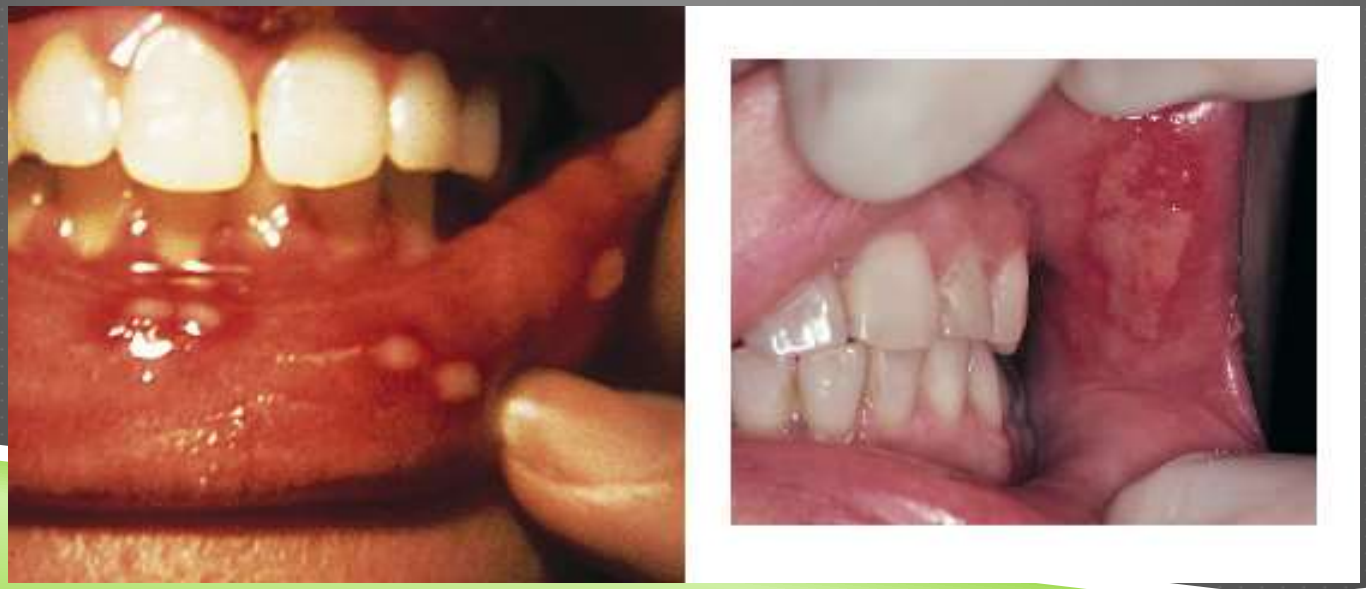
methotrexate, fluorouracil, cytarabine and the antitumor antibiotics

TREATMENT

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

PREVENTION

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



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 1mg 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
- Chemotherapy agents may partially or completely inhibit mitosis or impair metabolic processes in the hair matrix
- These effects can cause a thinned or weakened hair shaft or failure to form hair

Alopecia

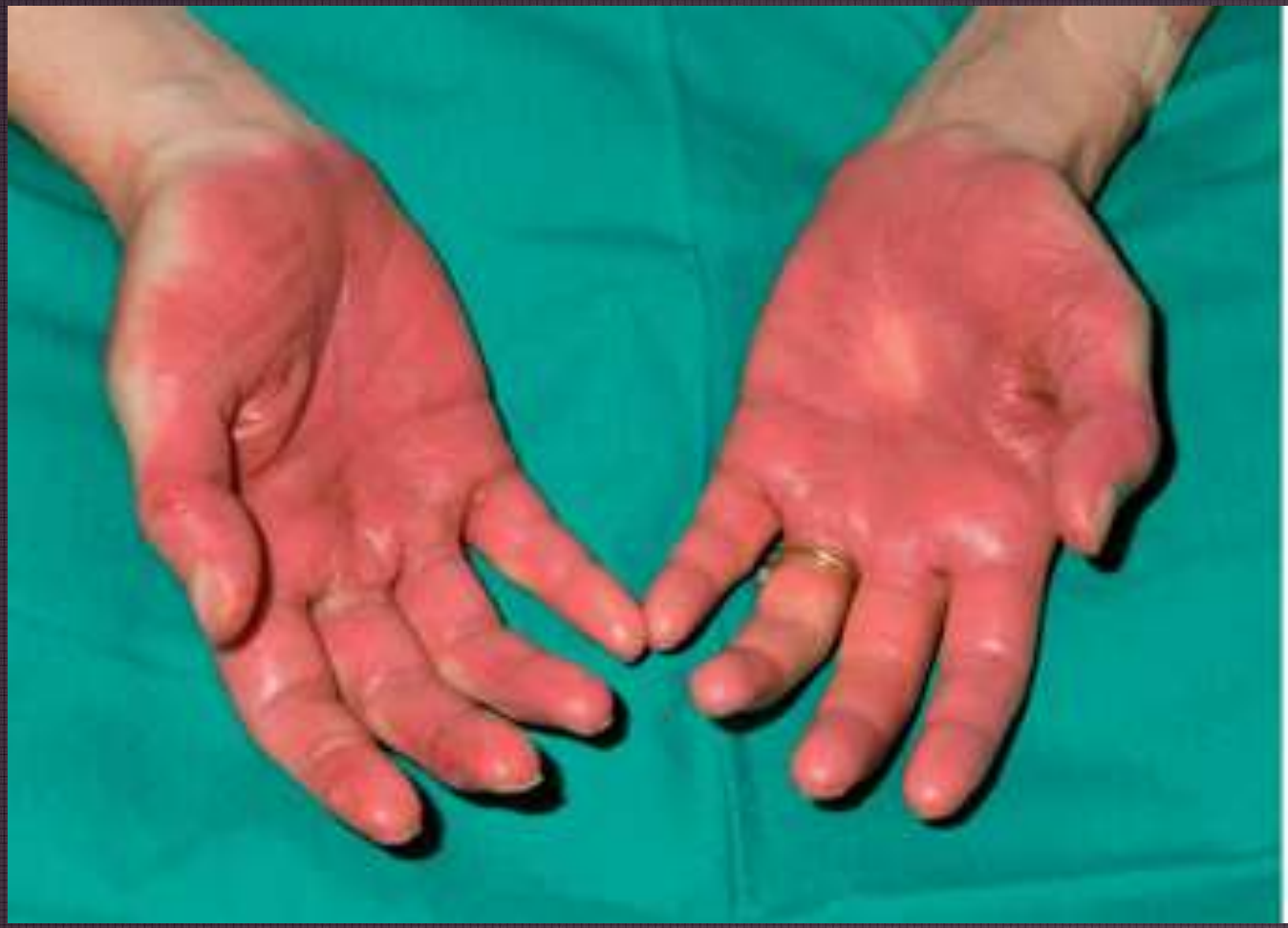
- Begins 7 to 10 days after one treatment, with prominent hair loss noted within 1 or 2 months.
- Reversible
- Regeneration 1 to 2 months after therapy completion
- The color and texture of hair may be altered; the new hair may be lighter, darker, or curlier as it regrows.

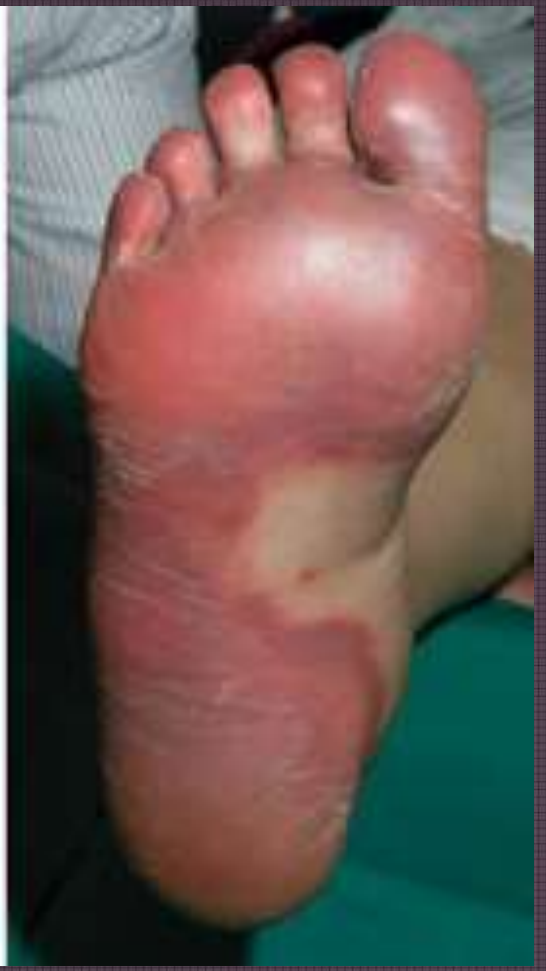
Hand-foot syndrome

- 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, docetaxel, capecitabine, sorafenib,sunitinib, pazopanib, regorafenib, axitinib, and vemurafenib

- Urea-based cream may be effective in prevention

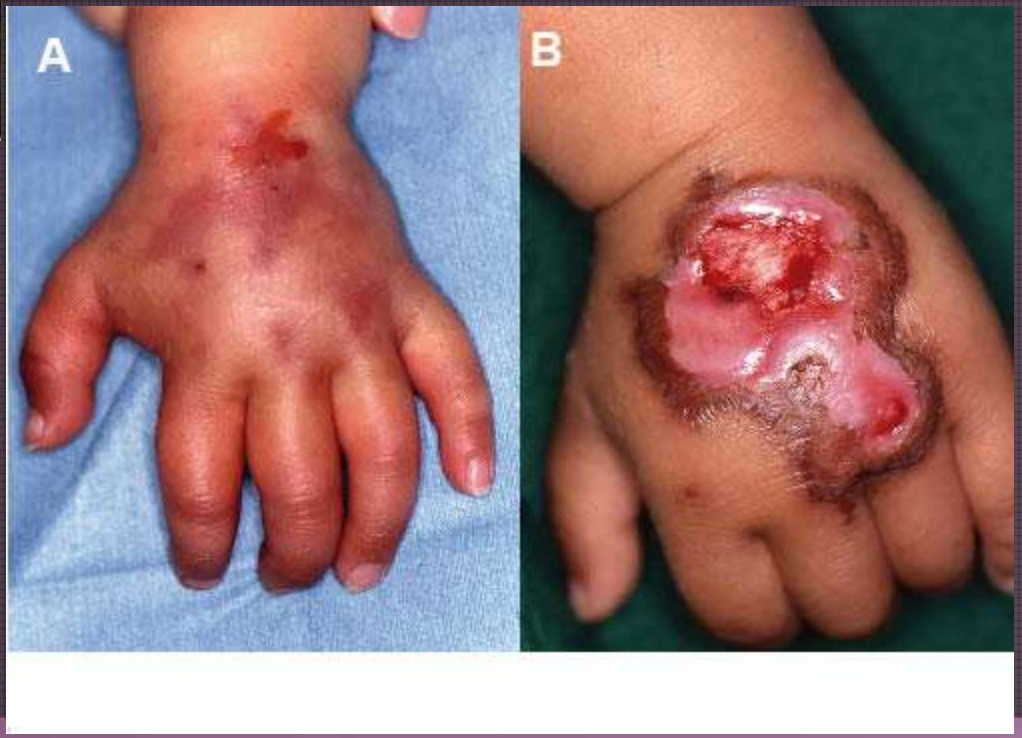
- Discontinuation of the medication will help to resolve the reaction





Irritant and vesicant reactions

- Transient local irritation
- Irritation of the vein
- Extravasation



Management

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

SPECIFIC ORGAN TOXICITIES

Neurotoxicity

- Methotrexate
  - High-dose IV methotrexate causes acute encephalopathy
  - Is usually transient and reversible
- High doses of cytarabine
  - Encephalopathy
  - Cerebellar dysfunction
  - Leukoencephalopathy
  -

- Asparaginase and PEG-aspargase
  - Encephalopathy
  - Stupor, coma, excessive somnolence, disorientation, hallucination, or severe depression

Peripheral neuropathy

- Vincristine
  - Paresthesia (numbness and tingling) involving the feet and hands
  - Pain and temperature sensory loss
  - Depression of deep tendon reflexes
  - Motor weakness with a foot drop or muscle atrophy

- Oxaliplatin
  - Hyperexcitability of peripheral nerves
  - Calcium and magnesium infusions

Autonomic neuropathy

- Vincristine & vinblastine
  - Colicky abdominal pain with or without constipation
    - Prophylactic laxatives
    - Senna derivatives or bisacodyl
  - Bladder atony with urinary retention
  - Impotence
  - Orthostatic hypotension

Cardiotoxicity

- Cardiomyopathy
  - Anthracycline
  - Formation 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

Other nephrotoxic agents

- Streptozocin , lomustine, carmustine, ifosfamide, pemetrexed and azacytidine
  - Proximal tubule dysfunction
  - loss of protein, glucose, bicarbonate, and potassium

Proteinuria

- Bevacizumab, an anti-VEGF 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

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

Hepatotoxicity

- 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