Principles of Chemotherapy

Dr Fatemeh Nejatifar

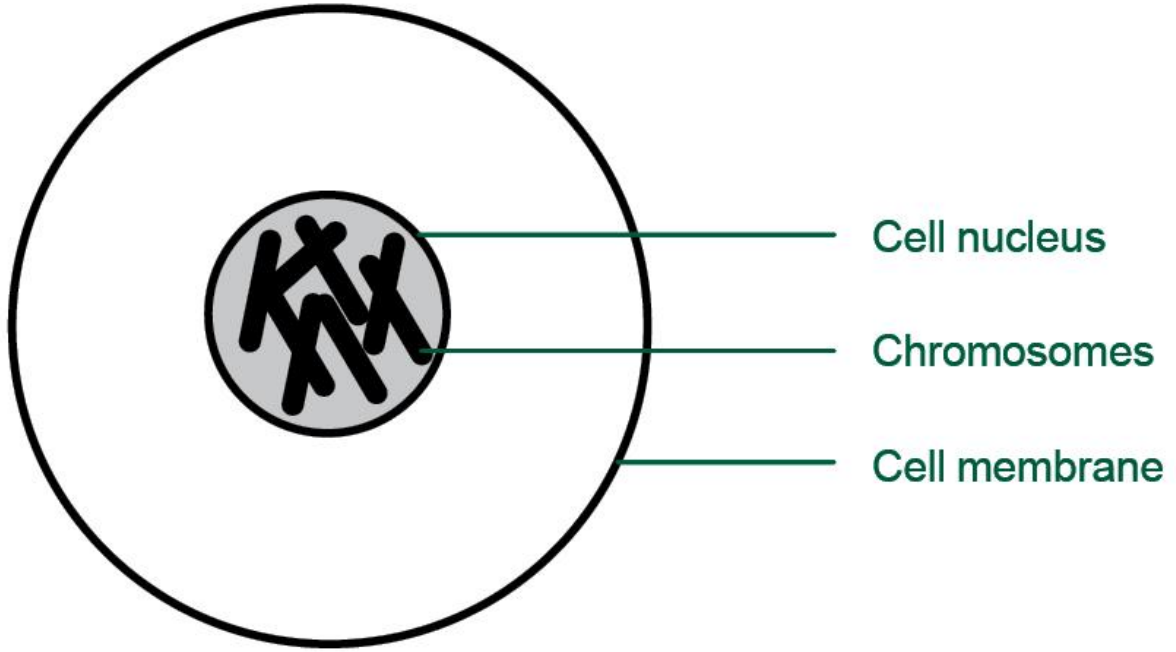
Hematologist & Medical Oncologist

Guilan University of Medical Sciences

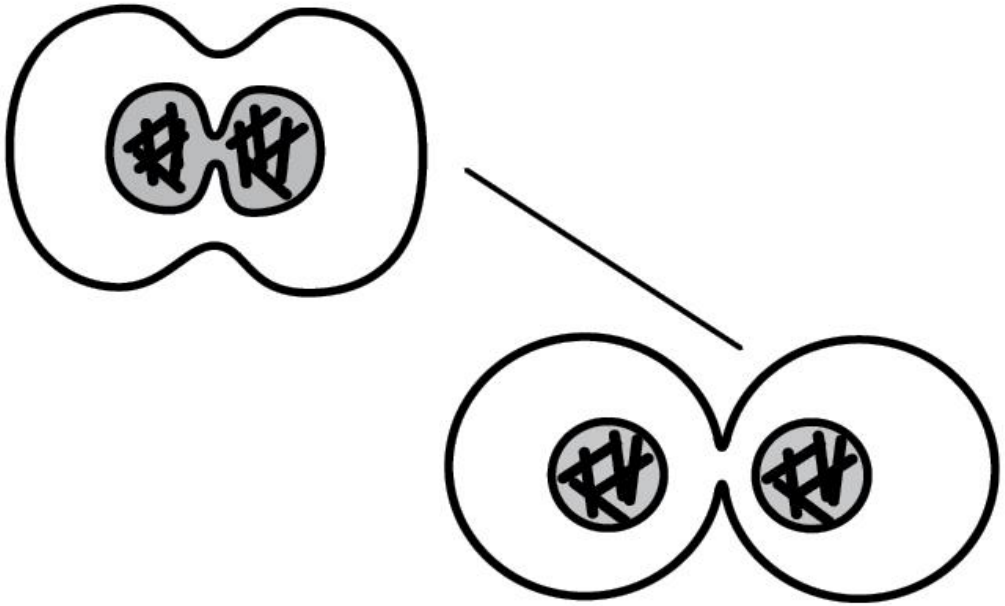
What is cancer?

- A condition where cells in a specific part of the body grow and reproduce uncontrollably.
- The cancerous cells can invade and destroy surrounding healthy tissue, including organs.

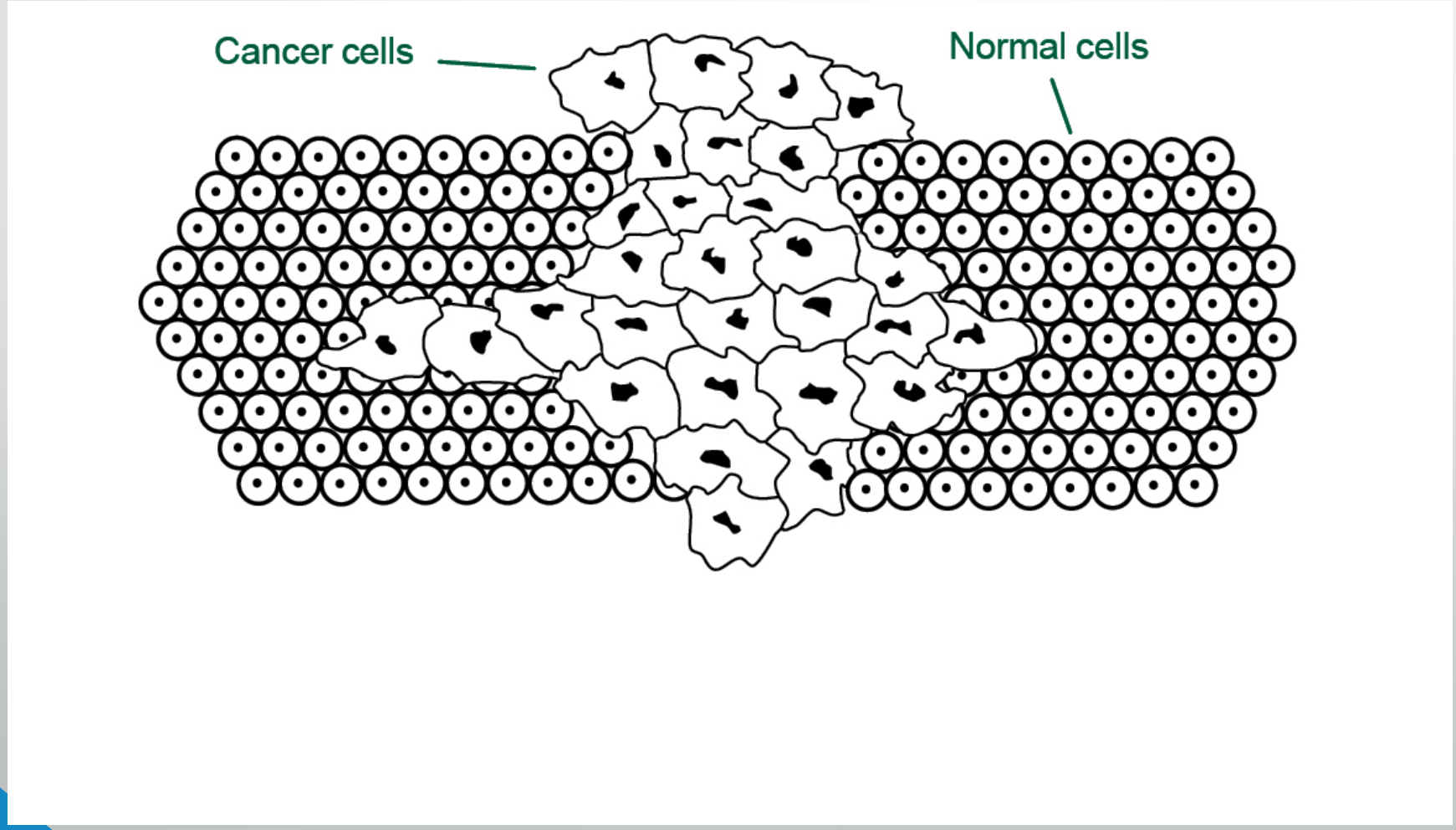
The normal cell



Normal cell dividing



Uncontrolled cell growth



Differences between normal and cancer cells

Normal cells:

1. Regulated cell division
2. Programmed cell death
3. Respond to external growth and anti-growth signals
4. Balance between blood vessel development and cell need
5. No tissue invasion.

Cancer cells:

1. Unregulated cell division
2. Lack programmed cell death
3. Generate own growth signals and insensitive to antigrowth signals
4. New blood vessel growth
5. Tissue invasion and metastasis.

Risk factors for getting cancer

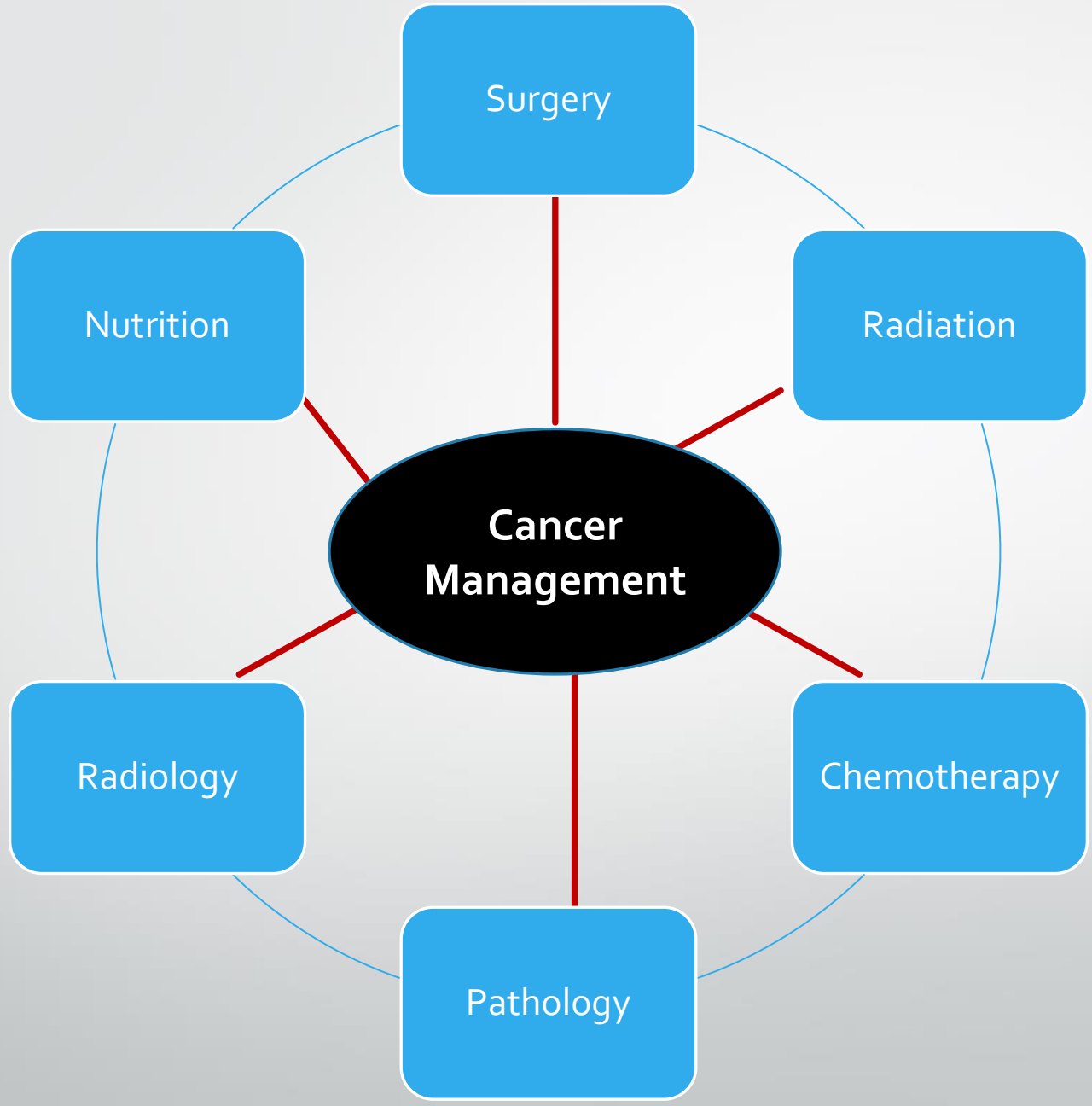
Main lifestyle risks:

- smoking
- being obese
- sun/sunbed
- alcohol
- lack of physical activity

Other risk factors

- age
- genetic
- environmental
- ethnicity

Ref:- World Cancer Research Fund (2007)


Surgery
Nutrition
Radiation
Cancer Management
Radiology
Chemotherapy
Pathology

CANCER CLINIC TEAM

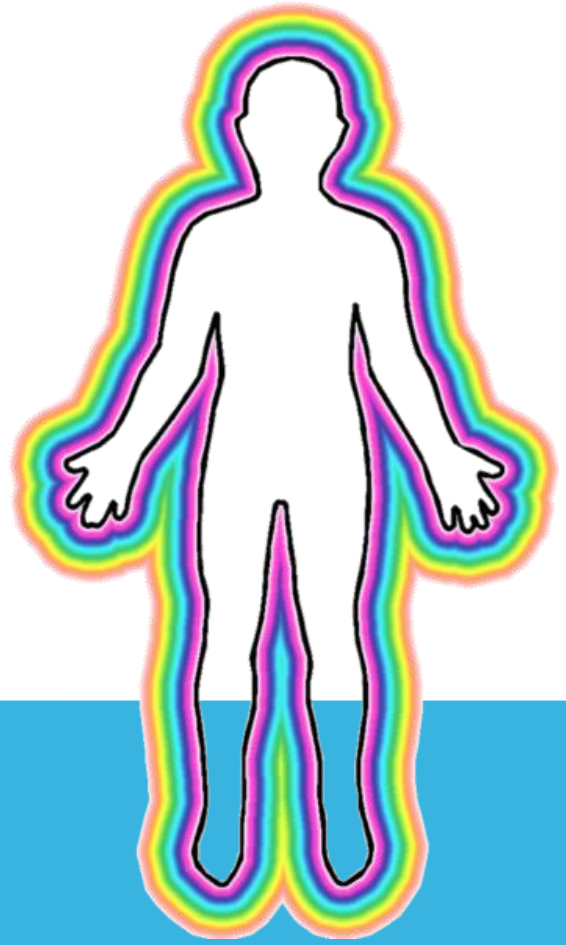
- Doctors
- Nurses (including Primary care and Treatment Room)
- Pharmacist
- Pharmacy Technician
- Social Worker
- Dietitian
- Clerks
- Volunteers

What is Chemotherapy?

- Medication given to treat cancer
- Systemic treatment
- Interfere with cancer cells' growth and replication
- Destroys the cancer cells

POSSIBLE SIDE EFFECTS

- Nausea
- Vomiting
- Diarrhea
- Constipation
- Mouth Sores
- Neuropathy
- Blood Clots
- Hair Loss



- Reduced Blood Cell Levels (Red Blood Cells, White Blood Cells, Platelets)
- Fatigue
- Fever
- Chemo “brain”/fog

NAUSEA

- ✓ Use anti-nausea medication as prescribed
- ✓ Sit upright after eating
- ✓ Eat small amounts more often
- ✓ Salty foods, crackers and dry toast may help
- ✓ Fresh air & exercise
- ✓ Avoid high acid and spicy foods

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (CINV)

Classification

- anticipatory
- acute
- delayed
- breakthrough
- refractory

Chemotherapeutic regimens can be classified as having high, moderate, low, or minimal risk of emetogenicity.

Incidence and timing of CINV vary according to patient factors and chemotherapeutic agents.

Incidence has been reported in as high as 70%–80% of patients.

Incidence of nausea > vomiting

antiemetic medications tend to be less effective in controlling nausea

- Important adverse effect of treatment
- Acute emesis: which most commonly begins within one to two hours of chemotherapy and usually peaks in four to six hours
- Delayed emesis: occurring more than 24 hours after chemotherapy
- Anticipatory emesis: occurring prior to treatment as a conditioned response in patients who have developed significant nausea and vomiting during previous cycles of chemotherapy

Table 3-1 Three categories of chemotherapy-induced nausea and vomiting

Acute nausea and vomiting
• Within the first 24 hours after chemotherapy
• Mainly by serotonin (5-HT) release from enterochromaffin cells
Delayed nausea and vomiting
• After 24 hours to 5 days after chemotherapy
• Various mechanisms: mainly substance P–mediated disruption of the blood-brain barrier and of gastrointestinal motility, adrenal hormones (9)
Anticipatory nausea and vomiting
• Occurrence is possible after one cycle of chemotherapy (8).
• Involves the element of classical conditioning

Adapted from (3).

Choosing the prophylactic strategy

- The three categories of drugs with the highest therapeutic index for the management of CINV:

- 5- hydroxytryptamine (5-HT3) receptor antagonists
- neurokinin-1 receptor (NK1R) antagonists
- glucocorticoids(especially dexamethasone)

5- hydroxytryptamine (5-HT3) receptor antagonists

- Ondansetron
- Oral 4mg
- Iv4mg/2ml & 8mg/4ml

- Granisetron
- Iv: 1mg/iml & 3mg/3ml

- .....

Ondansetron

- QT prolongation occurs in a dose-dependent manner and, specifically , at a single IV dose of 32 mg.
- QT interval prolongation is expected to be greater with a faster rate of infusion and larger doses for IV administration.

- avoid use of ondansetron in patients with congenital long QT syndrome

- to use ECG monitoring in certain patients, including those with hypokalemia or hypomagnesemia, heart failure, and bradyarrhythmias, and in patients taking other medications that increase the risk of QTc prolongation

Neurokinin-1 receptor antagonists

- The introduction of the NK1R antagonists aprepitant and fosaprepitant (a parenteral water-soluble prodrug of aprepitant that is effective as a one-day treatment has significantly improved the ability to prevent both acute and delayed CINV in patients receiving highly emetic, IV-administered chemotherapy

Olanzapine

- Olanzapine, a second-generation antipsychotic that blocks serotonin 5-hydroxytryptamine (5-HT2) receptors and dopamine D2 receptors, may be a particularly useful agent for the prevention of both acute and delayed nausea and vomiting

- Anticipatory nausea and emesis are conditioned responses that occur in patients who experienced severe nausea and vomiting during prior cycles of chemotherapy
- Nonpharmacologic methods (eg, hypnosis, behavioral therapy with systemic desensitization)
- low-dose alprazolam (0.5 to 2 mg/day)

Estimating the risk of nausea and vomiting

- The most important factor determining the likelihood of acute or delayed emesis developing during chemotherapy is the intrinsic emetogenicity of the particular agent.

Estimating the risk of nausea and vomiting

- Highly emetic – >90 percent risk of emesis
- Moderately emetic – >30 to 90 percent risk of emesis
- Low emetogenicity – 10 to 30 percent risk of emesis
- Minimally emetic – <10 percent risk of emesis

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Antiemesis

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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 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]

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]
C • Olanzapine 10 mg PO once[r,s,t] • 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]	C • Olanzapine 10 mg PO daily on days 2, 3, 4[r] • 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

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]
F Note: an NK-1RA should be added (to dexamethasone and a 5-HT3 RA regimen) for select patients with additional risk factors or previous treatment failure with a steroid + 5HT3 RA alone. See AE-5 • NK-1RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[k] ▸ Fosaprepitant 150 mg IV once[l] ▸ 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]	F • 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

Extravasations

- *Extravasation* *is the process of* *unintentional instillation of a given* infusion or injection, passing out of a vessel into surrounding tissue such as subcutaneous fat, underlying connective tissue, or muscle.

Risk factors

- Patient
- Drug
- Medical staff

Patient factors:

- Peripheral veins at the back of the hand, the dorsum of the foot, or the inside of an elbow are more vulnerable
- Older patients and patients with sclerosis or smaller vessels suffer more damage
- higher venous pressure following thrombosis, right cardiac insufficiency, mediastinal tumors, or a vena cava superior syndrome due to other reasons

- Patients with neurologic deficits like reduced sensitivity due to diabetes or chemotherapy- induced polyneuropathy may report extravasation too late, and this results in more extensive tissue damage.

- Insufficient puncture skills
- Overtired or too few personal
- time pressure
- The location of intravenous access
- Safety is highest with intravenous lines in the forearm and declines in this order from the back of the hand to the inside of the elbow.
- High-pressure infusions to peripheral veins, large volumes, and longer duration of infusion

Intravenous (IV) chemotherapy drugs

Vesicants: have the potential to cause a chemical burn if they inadvertently go into the tissue

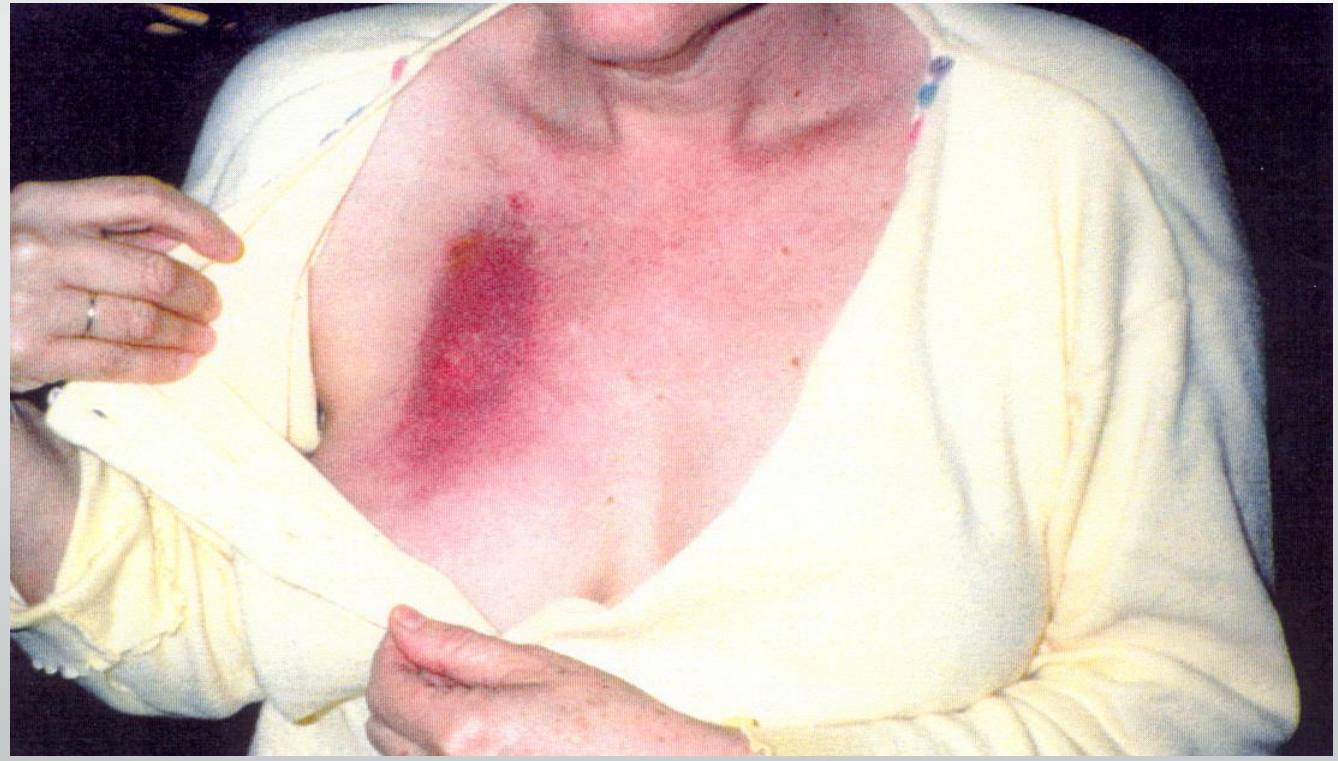
Non-vesicants: do not cause tissue damage

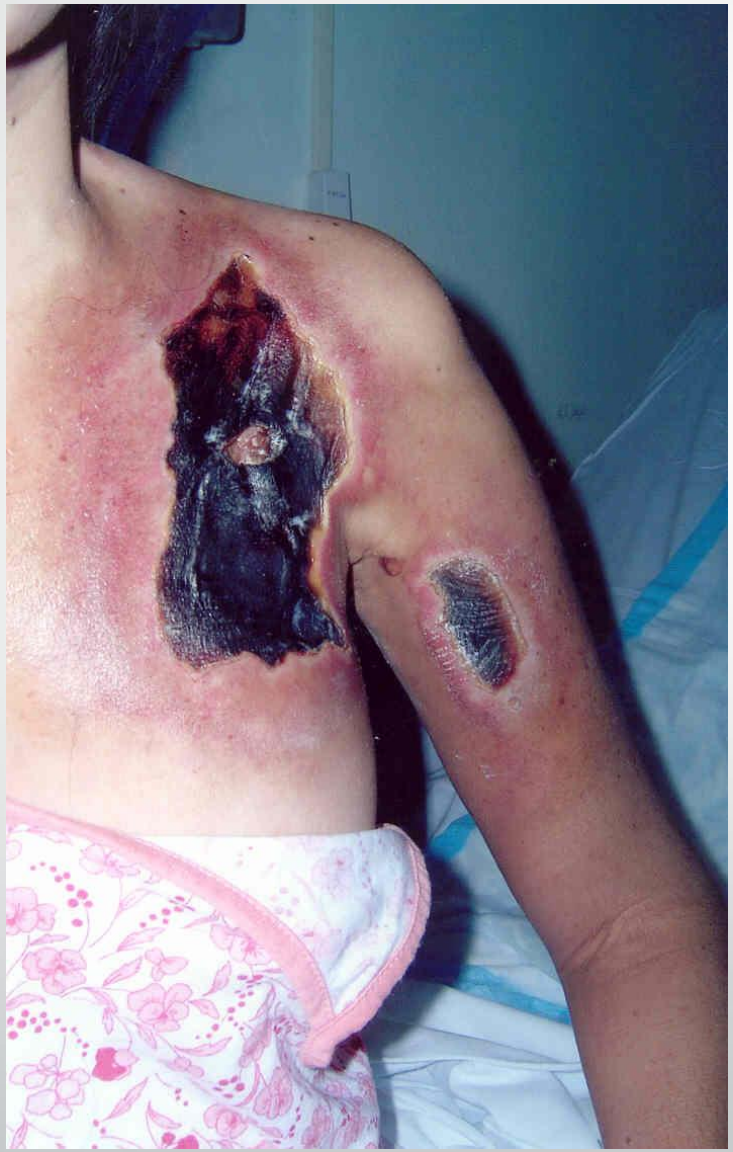
Vesicants
Amsacrine
Dactinomycin
Daunorubicin
Doxorubicin
Epirubicin
Idarubicin
Mechlorethamine
Mitomycin
Trabectedin
Vinblastine
Vincristine and liposomal vincristine
Vindesine
Vinorelbine

Irritants
Ado-trastuzumab emtansine*
Bendamustine¶
Bleomycin
Bortezomib
Busulfan
Carboplatin
Carmustine
Cisplatin$^{\Delta}$
Cladribine
Cyclophosphamide
Cytarabine
Dacarbazine$^{\Delta}$
Docetaxel

- An irritant drug causes an inflammatory reaction, with aching, burning, tightness, pain, and phlebitis at the needle insertion site or along the vein.

- warmth, erythema, and tenderness in the extravasated area, but without tissue sloughing or necrosis



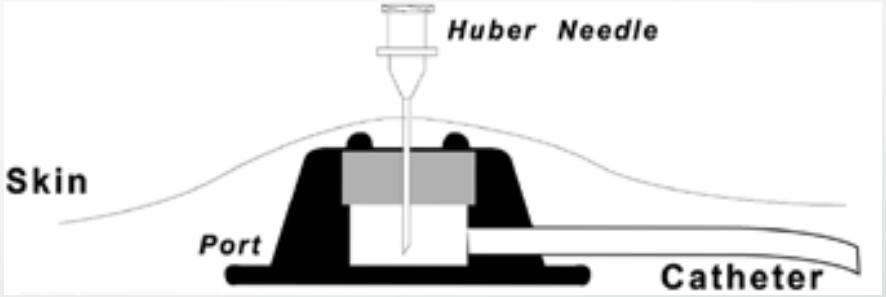


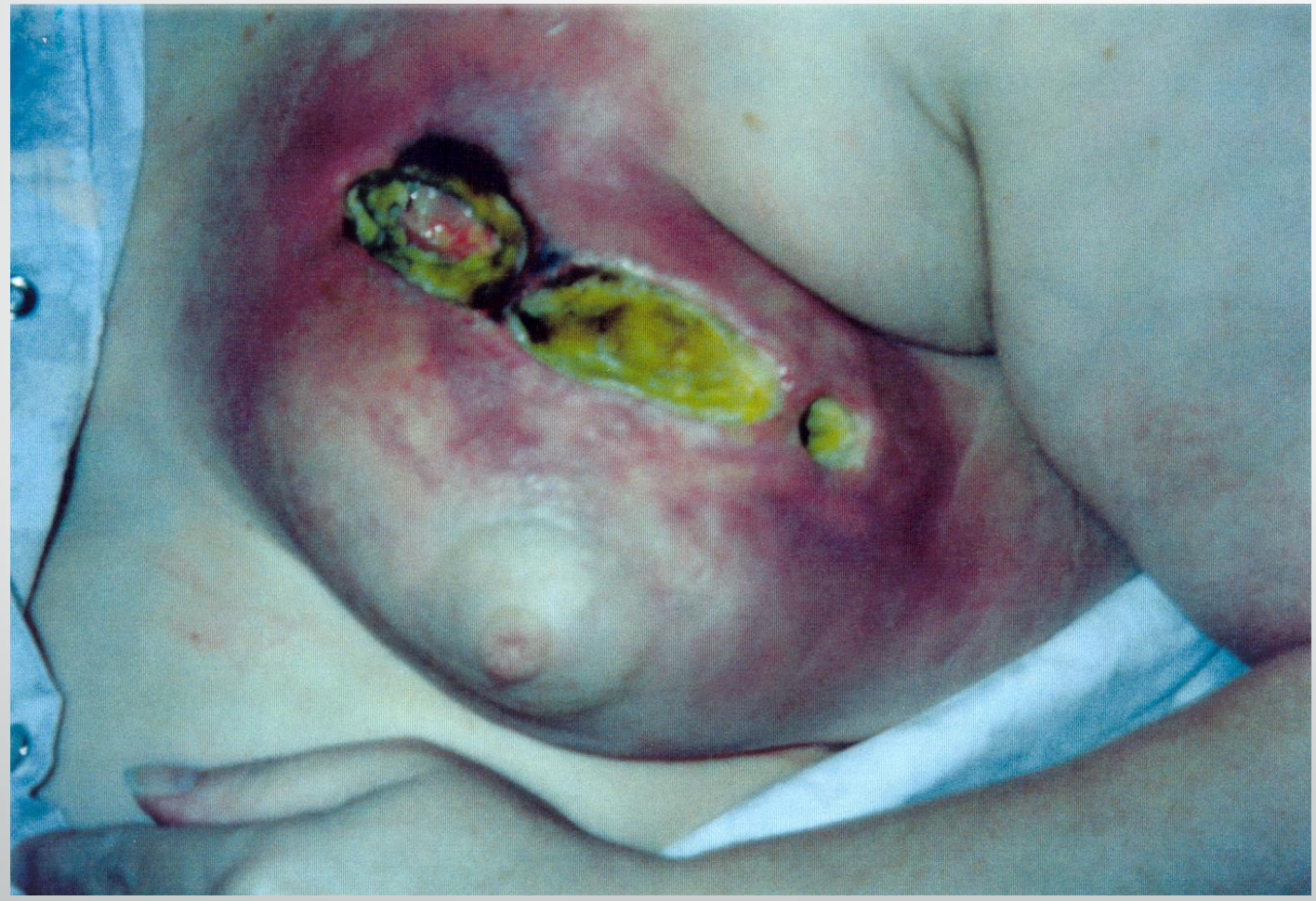
Extravasation of vesicant chemotherapy

May occur when:

---needles are incompletely placed into implanted ports

---needles dislodge from implanted ports

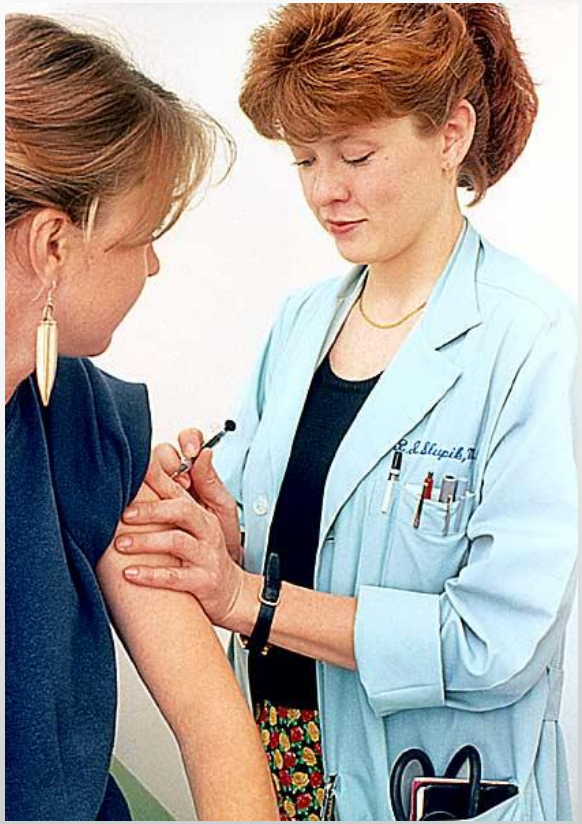




Extravasation of vesicant chemotherapy

Has occurred when:

---vesicants intended for IV administration have inadvertently been given IM or SQ



Not a device complication and not a vascular complication.

Prevention:

- For peripheral infusions of chemotherapy, the intravenous (IV) line should be recently started, and the vein selected should be large and intact, with good blood return established prior to starting the infusion

- Infusion sites should be selected in the following order of preference: forearm (basilic, cephalic, and median antebrachial), dorsum of hand, wrist, antecubital fossae. With vesicants, try to avoid the antecubital fossa, wrist, and dorsum of the hand, if at all possible.

- Sites with sclerosis, thrombosis, or scar formation should be avoided, as should limbs with impaired circulation.
- The butterfly needle or plastic cannula should be secured to the skin with tape.
- Taping of the entry site itself should be avoided so that the area can be examined.

- The patency of the IV line should be verified just prior to drug infusion by flushing with 5 to 10 mL of isotonic saline or a 5 percent dextrose solution.

- Instruct the patient to notify a clinician immediately if he or she experiences any pain, leaking, or other changes in sensation at the infusion site.

- The chemotherapeutic agent, appropriately diluted, should be infused through the side arm of the freely-flowing IV with isotonic saline or 5 percent dextrose.

- Previously irradiated areas should be avoided whenever possible.

- Stop the infusion immediately.
- Do not flush the line, and avoid applying pressure to the extravasated site.
- Elevate the affected extremity.
- The catheter/needle should **not be removed immediately** **.Instead, it should be left in place to attempt to aspirate** fluid from the extravasated area and to facilitate the administration of an antidote to the local area, if appropriate
- If an antidote will not be injected into the extravasation site, the catheter/needle can be removed after attempted aspiration of the subcutaneous tissues.

PHARMACOLOGIC MANAGEMENT

- **AMSACRINE, MITOMYCIN C,MITOXANTRONE, DACTINOMYCIN:**
- Extravasation of these substances demands immediate dry local cooling for at least 1 hour and continuation for some days several times daily, 15 minutes each time.
- Topical use of dimethylsulfoxide (DMSO) 99% 4 to 6 times daily is recommended for at least 7 days

- ***VINCA ALKALOIDS AND ETOPOSIDE***:

- Perilesional hyaluronidase is injected subcutaneously or intradermally (1500 IU/ml in 10 ml NaCl), starting from the periphery and moving toward the center.

- Specific measures include dry heat (no hot humidity!) for 1 hour the first time, then 4 times daily for 20 minutes each time

Specific antidotes

- Systemic administration of dexrazoxane following anthracycline extravasation
- Topical application of dimethylsulfoxide (DMSO) for anthracycline extravasation when dexrazoxane is not immediately available
- Local injection of hyaluronidase for extravasations of vinca alkaloids, paclitaxel, epipodophyllotoxins, and ifosfamide

- corticosteroids are not indicated in the management of vesicant extravasations, with the possible exception of large-volume extravasations of oxaliplatin

- Corticosteroids may worsen the skin damage from etoposide or vinca alkaloids, and they are specifically contraindicated in these situations

Oral Mucositis

- Definition- A disorder characterized by inflammation of the oral mucosal

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences urgent intervention indicated	Death

Preventing Mouth Sores

- ✓ Frequent rinsing
- ✓ Rinse mouth with baking soda and water or salt and water 3 – 4 times/day
- ✓ Remove dentures
- ✓ Avoid alcohol-containing commercial mouthwashes
- ✓ Drink lots of fluids
- ✓ Avoid spicy and acidic foods

Treating Mouth Sores

- ✓ Soft foods, high in calories and protein
- ✓ Yogurt, pudding, milkshakes, custard, watermelon
- ✓ Medication can be prescribed

Allergic reactions to chemotherapy

- The cytotoxic agents that are most commonly associated with infusion reactions are the taxanes , platinum drugs, pegylated liposomal doxorubicin, L-asparaginase ,procarbazine, etoposide, bleomycin, cytarabine, and ixabepilone.

Signs and symptoms of anaphylaxis

- platinum drugs and the taxanes can cause anaphylaxis
- Cutaneous symptoms: flushing, itching, urticaria , and/or angioedema (usually of face, eyelids, or lips)
- Respiratory symptoms: repetitive cough, sudden nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality (due to laryngeal edema), hypoxia

- Cardiovascular symptoms: faintness, tachycardia (or less often bradycardia), hypotension, hypertension and/or loss of consciousness

- Gastrointestinal symptoms: nausea, vomiting, abdominal cramping, and/or diarrhea

- Neuromuscular symptoms: sense of impending doom, tunnel vision, dizziness, and/or seizure, severe back, chest, pelvic pain

Promptly and simultaneously, give:

- **IM epinephrine (1 mg/mL preparation): Give epinephrine 0.3 to 0.5 mg intramuscularly, preferably in** the mid-outer thigh. Can repeat every 5 to 15 minutes (or more frequently), as needed.

- If epinephrine is injected promptly IM, most patients respond to one, two, or at most, three doses.

- If symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion

- **Place patient in recumbent position, if tolerated, and elevate lower extremities.**
- **Oxygen: Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed.**
- **Normal saline rapid bolus: Treat hypotension with rapid infusion of 1 to 2 liters IV. Repeat, as needed.**
- Massive fluid shifts with severe loss of intravascular volume can occur.

- **Albuterol (salbutamol): For bronchospasm resistant to IM epinephrine, give 2.5 to 5 mg in 3 mL saline** via nebulizer. Repeat, as needed.

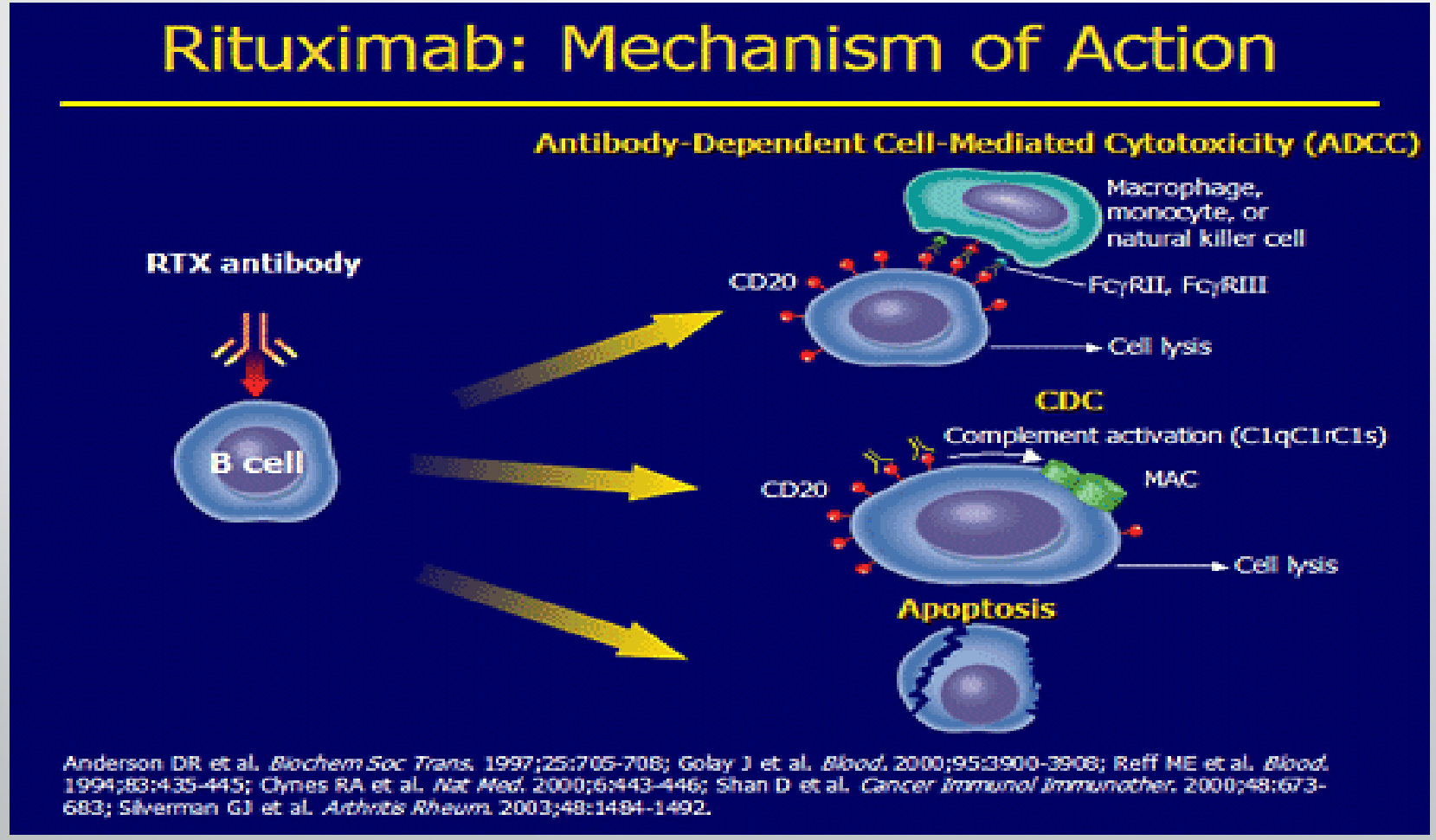
Targeted Therapies!

Monoclonal antibodies

Targeted therapies

Immunotherapies

Monoclonal antibodies



Do not administer IV push or bolus.

Do not administer IV rituximab subcutaneously.

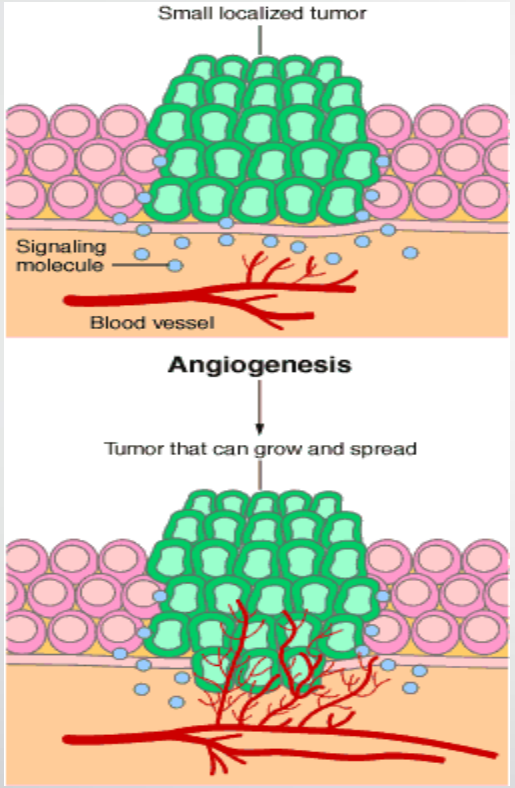
If an infusion-related reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate. Discontinue infusion in the event of serious or life-threatening cardiac arrhythmias.

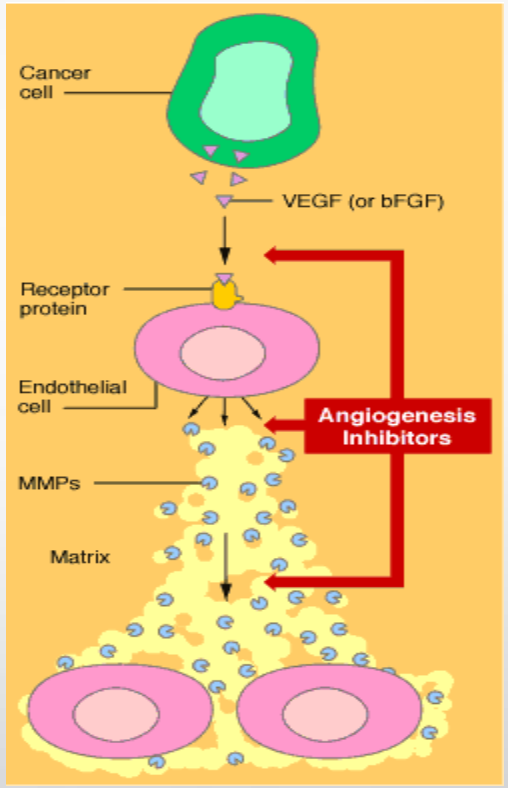
Initial infusion: Start infusion at a rate of 50 mg/hour; if there is no infusion-related reaction, increase the rate by 50 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour

- Standard infusion rate: If patient tolerated initial infusion, start at 100 mg/hour; if there is no infusion-related reaction, increase the rate by 100 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour

- Accelerated infusion rate (90 minutes): For patients with previously untreated follicular NHL and diffuse large B cell NHL who are receiving a corticosteroid as part of their combination chemotherapy regimen, have a circulating lymphocyte count <5,000/mm3 or have no significant cardiovascular disease.
- After tolerance has been established (no grade 3 or 4 infusion-related event) at the recommended infusion rate in cycle 1, a rapid infusion rate may be used beginning with cycle 2.

Angiogenesis in tumors





Bevacizumab

- Improve survival in:
  - Colon cancer
  - Lung cancer
  - Renal cancer

Adverse Effects

- Most common adverse reactions (>10% and at least twice the control rate arm)
  - Epistaxis
  - Headache
  - Hypertension
  - Rhinitis
  - Proteinuria
  - Taste alteration
  - Dry skin
  - Rectal hemorrhage
  - Lacrimation disorder
  - Back pain
  - Exfoliative dermatitis

Cautions

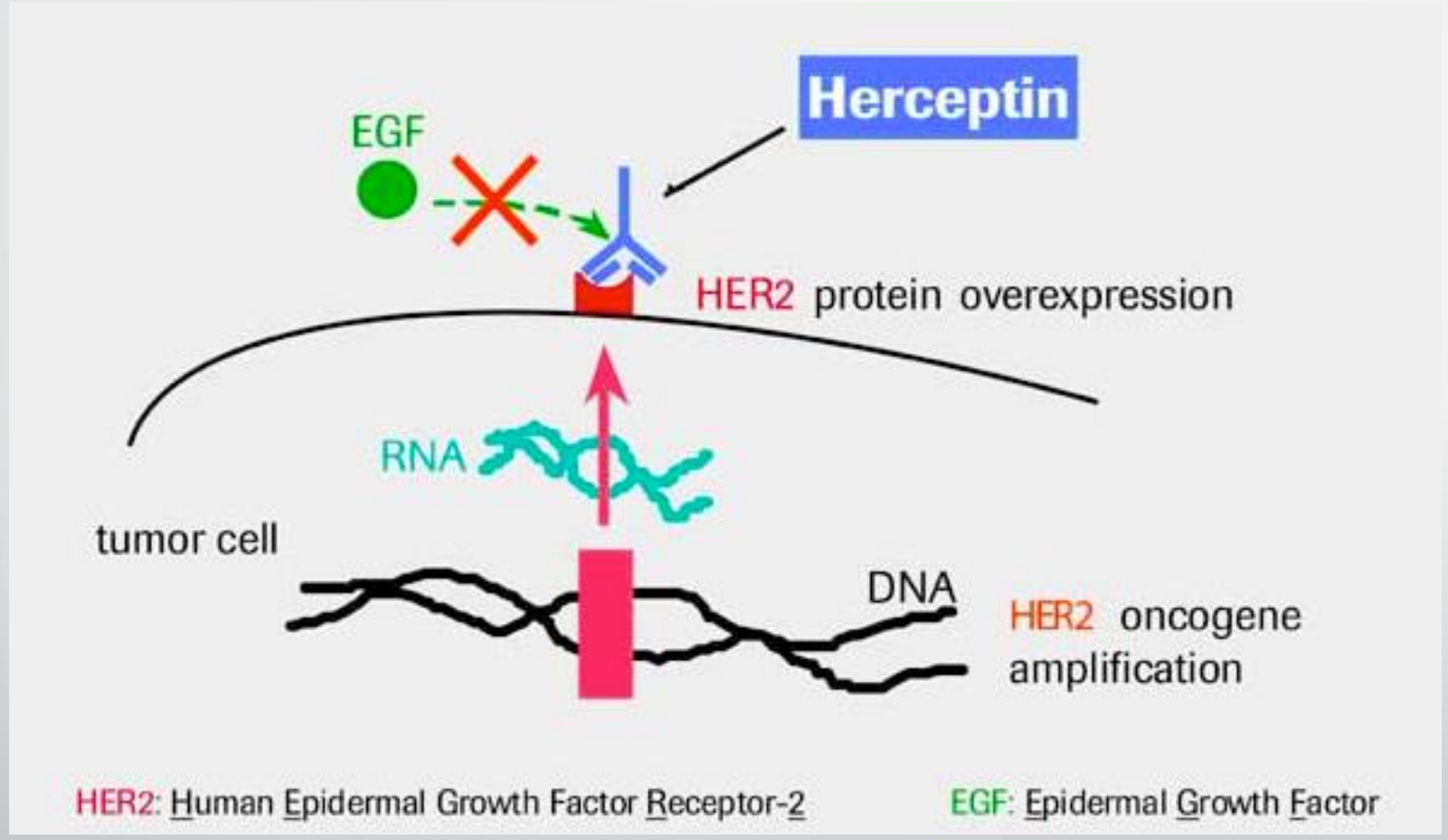
- Perforation or fistula
  - Discontinue Avastin if perforation or fistula occurs
- Arterial thromboembolic events
  - Discontinue Avastin for severe arterial thromboembolic events
- Venous thromboembolic events
  - Discontinue Avastin for life-threatening venous thromboembolic events
- Hypertension
  - Monitor blood pressure and treat hypertension
  - Temporarily suspend Avastin if not medically controlled
  - Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy

Cautions (continued)

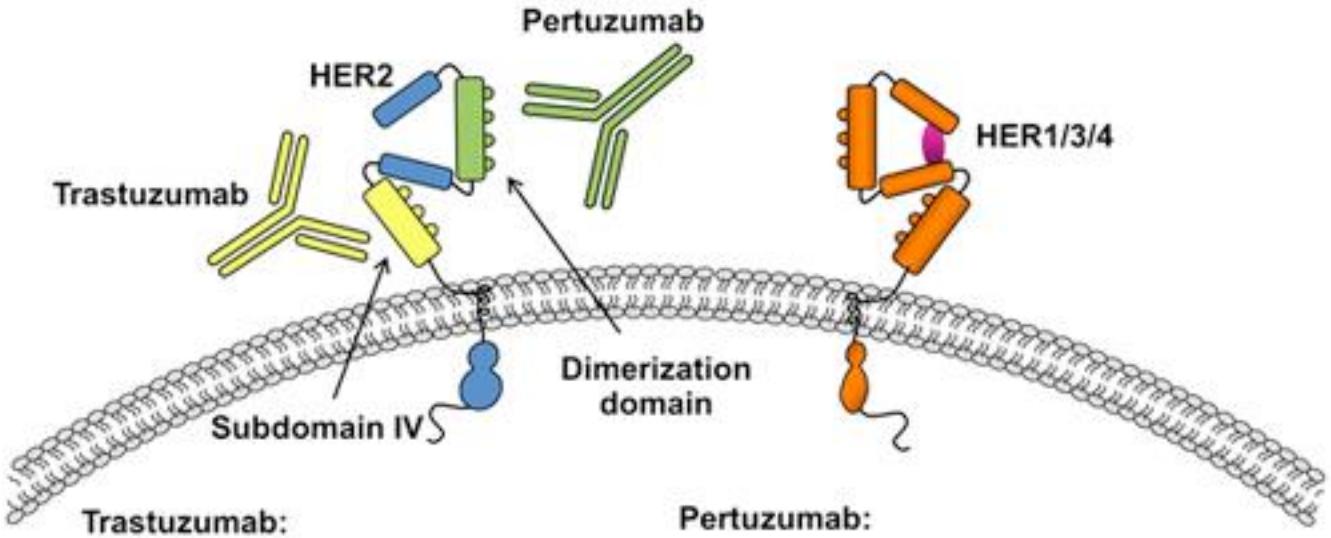
- Posterior reversible encephalopathy syndrome (PRES)
  - Discontinue bevacizumab
- Proteinuria
  - Monitor urine protein
  - Discontinue bevacizumab for nephrotic syndrome
  - Temporarily suspend bevacizumab for moderate proteinuria
- Infusion reactions
  - Stop bevacizumab for severe infusion reactions
- Ovarian failure
  - Inform females of reproductive potential of the risk of ovarian failure with bevacizumab

HER-2 A Target for Breast Cancer

- Human epidermal growth factor receptor 2
- Overexpressed in 25% of breast cancers
- Historically associated with more aggressive course


Herceptin
EGF
HER2 protein overexpression
RNA
tumor cell
DNA
HER2 oncogene amplification
HER2: Human Epidermal Growth Factor Receptor-2
EGF: Epidermal Growth Factor

Pertuzumab and Trastuzumab
Complementary Mechanisms of Action



Trastuzumab:

- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

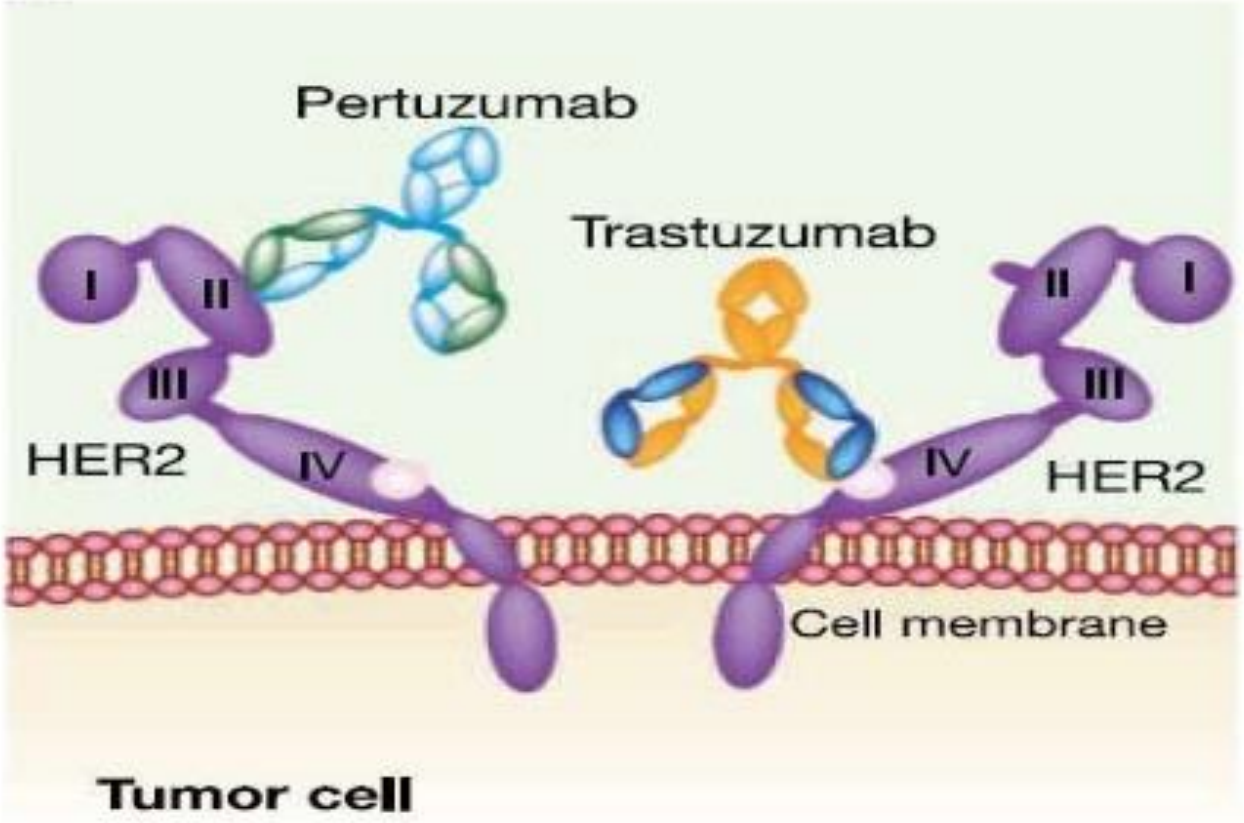
Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Baselga J, et al.[5]

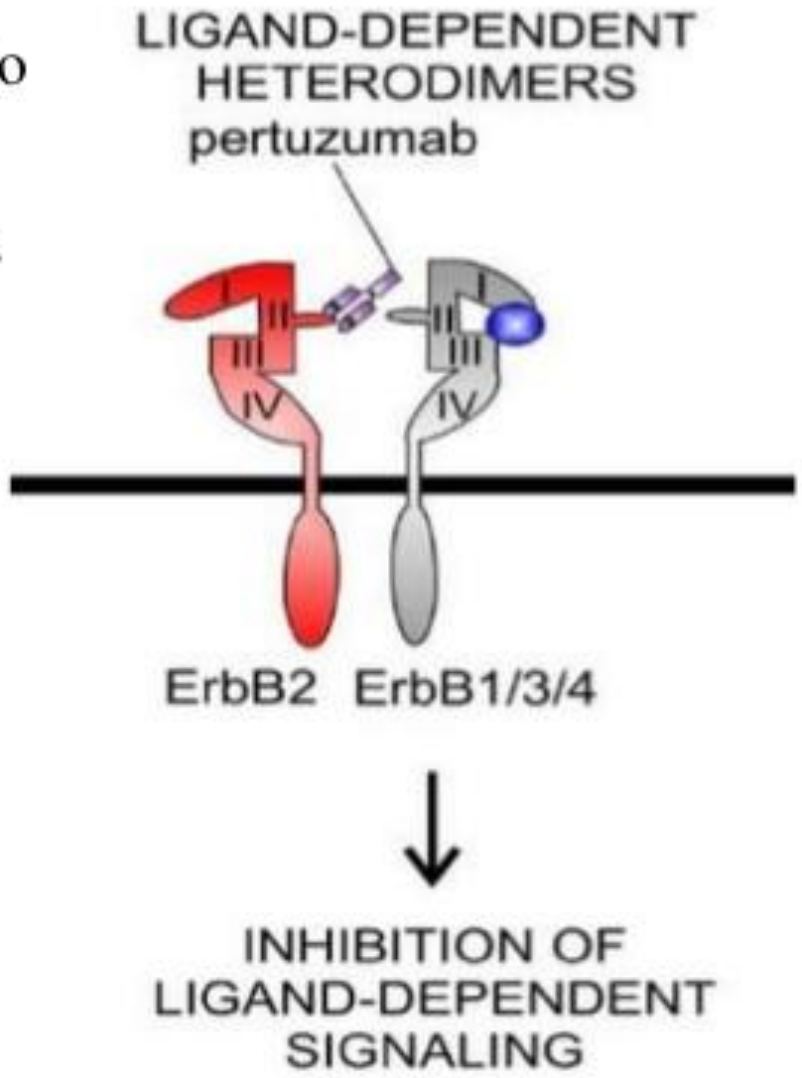
PERTUZUMAB

- Pertuzumab (Perjeta) is a humanized IgG1 MAb that binds to domain II of HER2 and blocks ligand- dependent dimerization of HER2 with other members of the EGFR family.



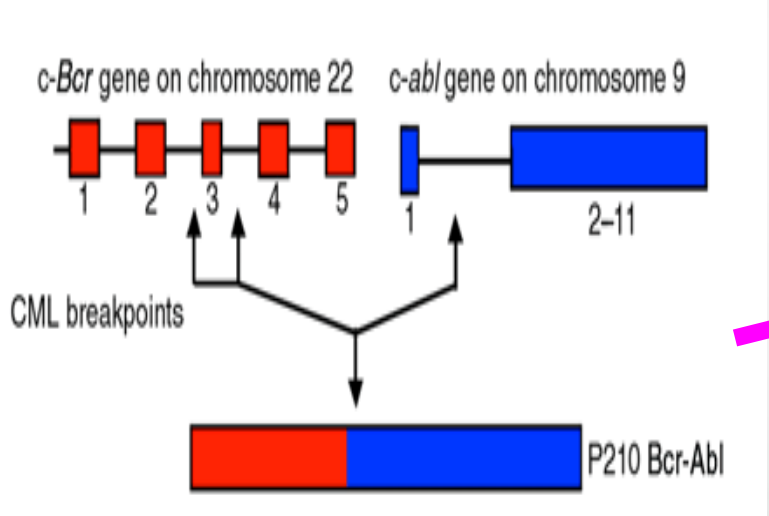
Mechanism of action

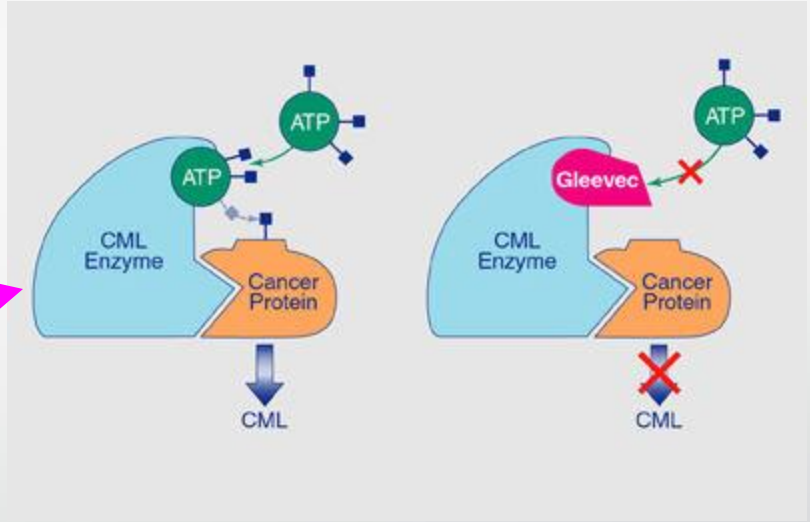
- Binding of pertuzumab to Her2 leads to inhibition of heterodimerisation of Her2 with other 'Her' family members
- Inhibition of these heterodimerisation process leads to inhibition of downstream signalling pathways- MAPK,PI3K,this cell apoptosis
- ADCC



Targeted therapy

(Imatinib)





Source: Food and Drug Administration (FDA), Center for Drug Evaluation and Research

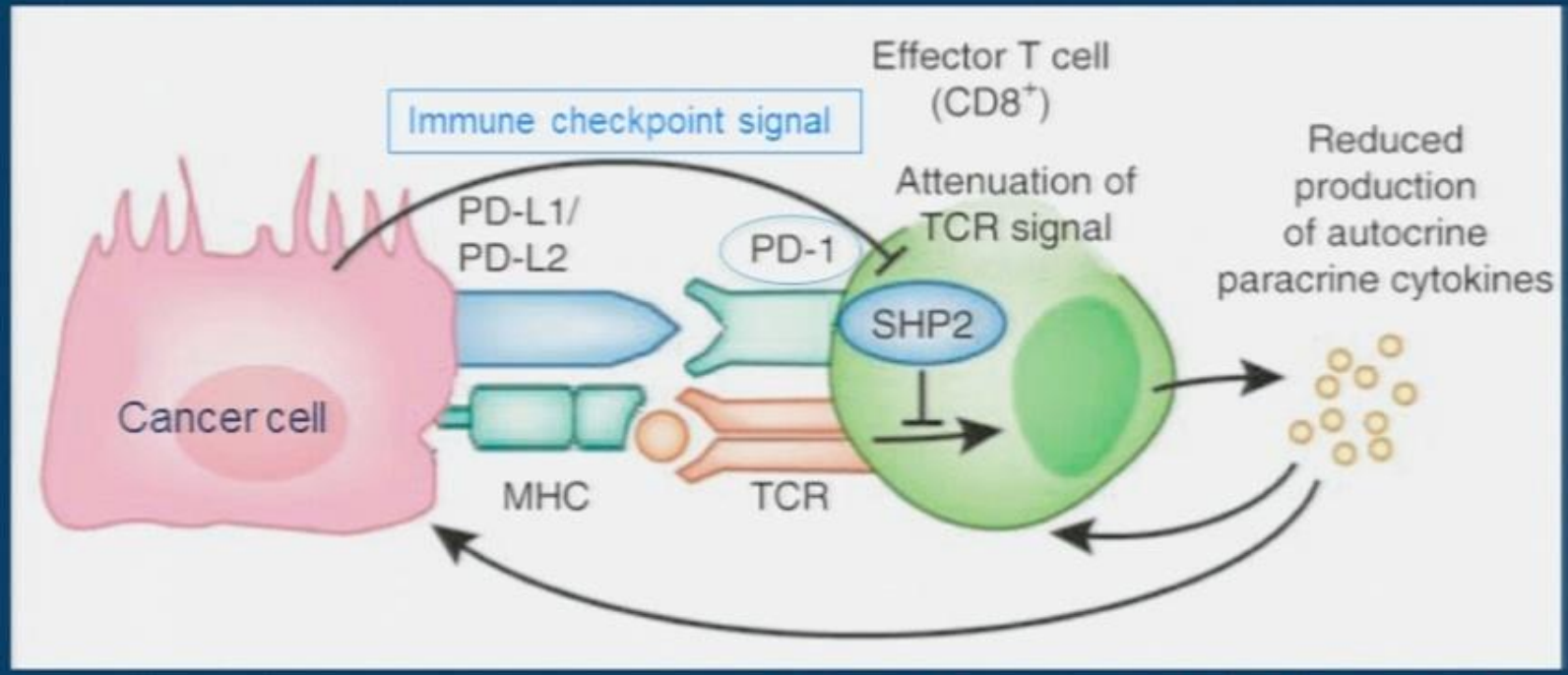
FDA-approved monoclonal antibodies for cancer treatment

Name of drug	**Type of cancer it treats**
Alemtuzumab (Campath)	Chronic lymphocytic leukemia
Bevacizumab (Avastin)	Brain cancer Colon cancer Kidney cancer Lung cancer
Cetuximab (Erbitux)	Colon cancer Head and neck cancers
Ibritumomab (Zevalin)	Non-Hodgkin's lymphoma
Ofatumumab (Arzerra)	Chronic lymphocytic leukemia
Panitumumab (Vectibix)	Colon cancer
Rituximab (Rituxan)	Chronic lymphocytic leukemia Non-Hodgkin's lymphoma
Tositumomab (Bexxar)	Non-Hodgkin's lymphoma
Trastuzumab (Herceptin)	Breast cancer Stomach cancer

Programmed Cell Death Protein 1 (PD-1)

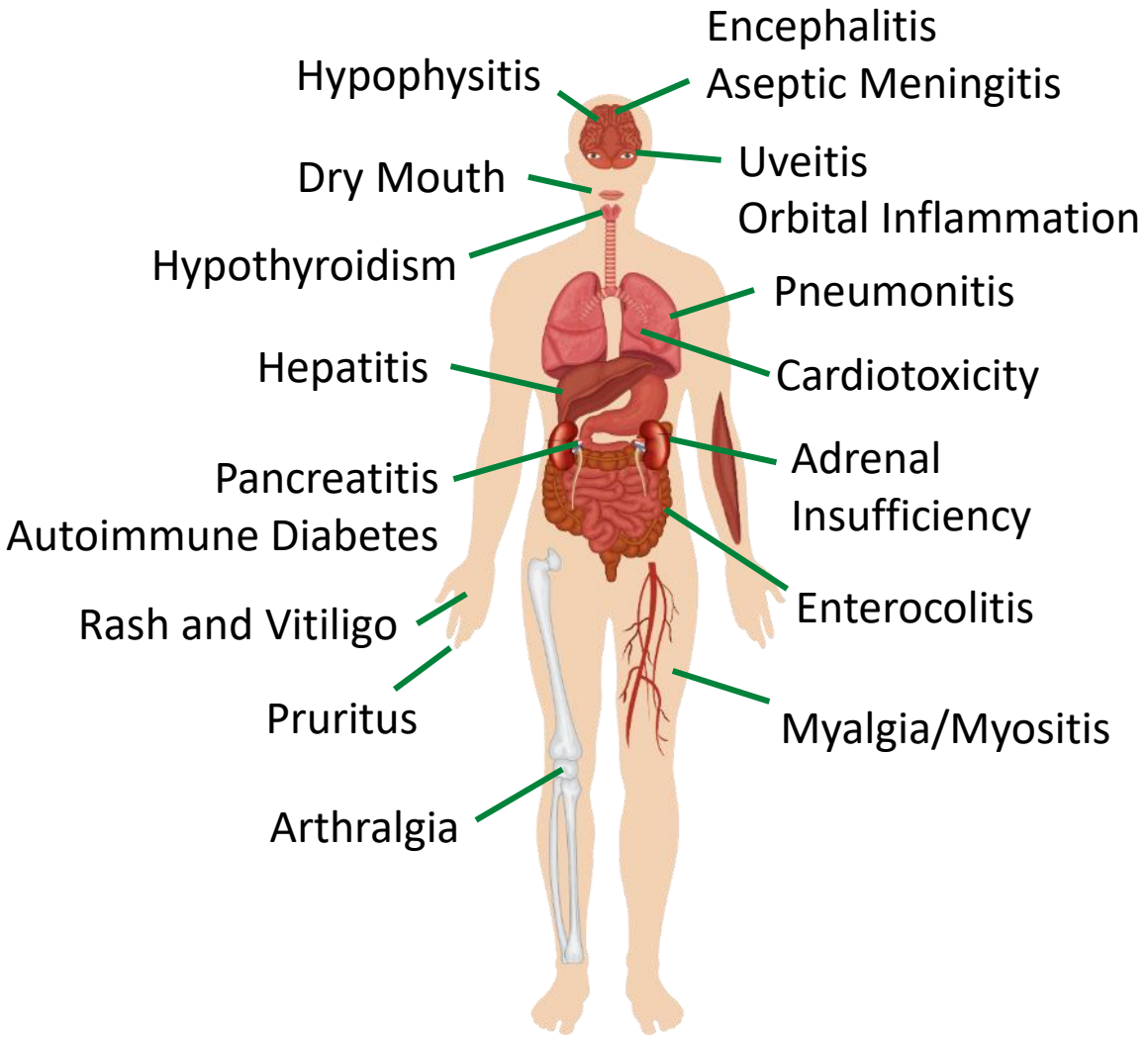
- New class of drug are inhibitors that activate immune system to attack tumors
- Pembrolizumab FDA approved Sept 2014 for metastatic melanoma
- Nivolumab FDA approved Dec 2014 for metastatic melanoma

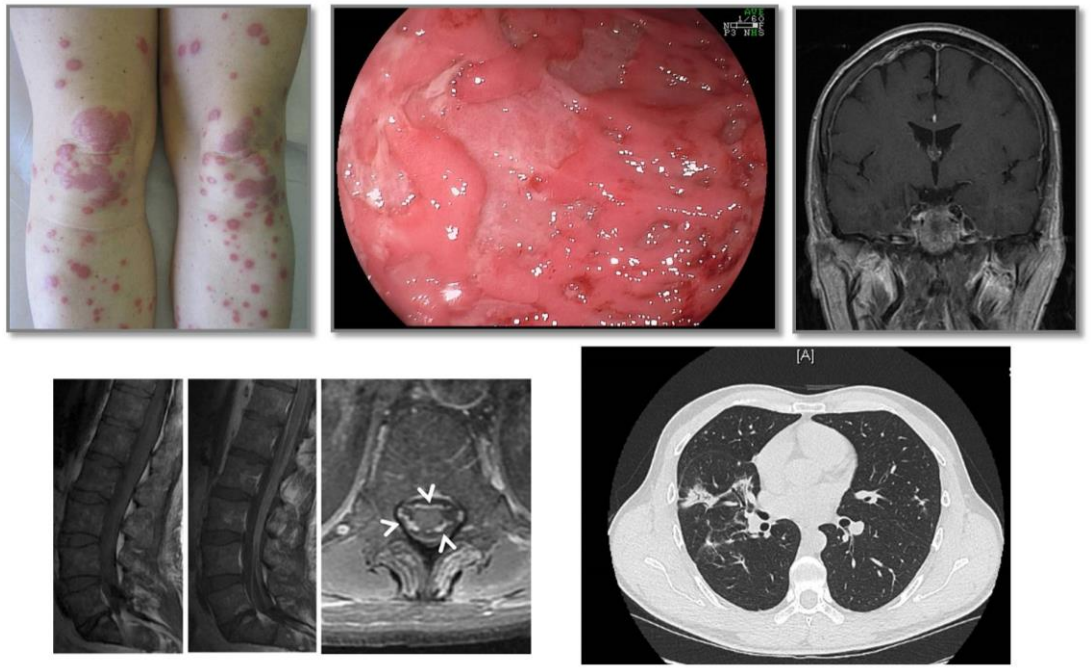
PD-1/ PD-L1 pathway in suppressing anti-tumor immunity



(Okazaki, Honjo et al. Nat Rev Immunol 2013, modified)

A New Spectrum of Adverse Events





Michot. Eur J Cancer. 2016;54:139. Steven. Rheumatology (Oxford). 2019;58(Suppl 7):vii29. Robert. ASCO 2017. Education session: Checkpoint inhibitor immunotherapy. Clinical images reproduced with permission of Dr. Caroline Robert, MD, PhD.

Slide credit: clinicaloptions.com

Patterns of irAEs

- **Onset**
  - Median onset is 5-12 wk after initiation
    - Within days of first dose
    - After months of treatment
    - After discontinuation of therapy
- **Severity**
  - Incidence/severity higher with anti–CTLA-4 agents
  - High-grade AE with one ICI class does not preclude safe administration with another ICI class

Davies. Immunotargets Ther. 2017;6:51. J Immunother Cancer. 2017;5:95. Martins. Nat Rev Clin Oncol. 2019;16:563.

Typical Presentations of Common irAEs

Common irAE	Typical Presentation
Dermatologic[1,2]	Maculopapular rash with or without pruritus, predominantly on trunk and to lesser extent the upper limbs, spreading to extremities; eczematous, lichenoid, psoriasiform manifestations; blistering skin reactions
Diarrhea/colitis[2]	Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting
Hepatic[2]	Often asymptomatic and diagnosed via routine blood tests
Pancreatic[1]	Asymptomatic elevation in amylase/lipase; CT, clinical findings of pancreatitis; severe abdominal pain, vomiting, and hemodynamically unstable
Endocrine[2,3]	Headaches, visual disturbances, fatigue, altered consciousness, deranged electrolytes (particularly hyponatremia), mood changes

1. Sibaud. Am J Clin Dermatol. 2018;19:345. 2. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372. 3. Sznol. Cancer Treat Rev. 2017;58:70.

Less Common irAEs: Presenting Signs and Symptoms

Less Common irAE	Typical Presentation
Pneumonitis[1]	Dyspnea, cough, fever, chest pain
Renal[2]	Elevated serum creatinine; azotemia; inability to maintain acid–base or electrolyte balance; urine output change; edema
Ocular[2]	Vision changes; photophobia; tenderness/pain; eyelid swelling; proptosis; red/purple discoloration; eye redness
Neurologic[2]	Progressive or fluctuating muscle weakness, usually proximal to distal; absent/reduced deep tendon reflexes; sensory–motor deficit; headache, photophobia, neck stiffness with nausea/vomiting; confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality
Cardiovascular[3]	Generalized malaise and fatigue; dyspnea; edema; decreased ejection fraction on ECHO
Musculoskeletal[4]	Joint pain, swelling; inflammatory symptoms; stiffness after inactivity; improvement with heat; myalgias; myositis

1. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372. 2. Spiers. Rheumatology (Oxford). 2019;58(suppl 7):vii7.
3. Brumbaugh. Cardiol Rev. 2019;27:97. 4. Steven. Rheumatology (Oxford). 2019;58(Suppl 7):vii29.

General Guidelines for Management of irAEs

- **Grade 1: asymptomatic to mild symptoms**
  - Observation
  - Supportive care
  - Continue ICI therapy
- **Grade 2: moderate symptoms**
  - Local or noninvasive intervention indicated
  - Withhold ICI, consider redose if toxicity resolves to grade ≤1
  - Low-dose corticosteroids likely needed
  - May be able to continue treatment
- **Grade 3: medically significant but not immediately life-threatening**
  - Stop ICI immediately
  - Hospitalization indicated
  - High-dose steroids indicated
  - Slow steroid taper over ≥1 mo once toxicity resolves to grade ≤1
- **Grade 4: life-threatening consequences**
  - Urgent intervention
  - Permanently discontinue ICI therapy

- Consult promptly with relevant specialists for affected organ systems
- Dose reduction of ICI is NOT a recommended strategy

Atezolizumab adverse reaction management brochure. Nivolumab adverse reaction management guide. Pembrolizumab adverse reaction management guide.

Slide credit: clinicaloptions.com

Any Questions?