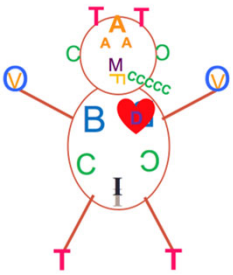
Toxicity of Traditional Chemotherapy & Targeted Therapy



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Allina Health | ABBOTT NORTHWESTERN HOSPITAL

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Disclosure

The presenter has no conflicts of interest to disclose

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Objectives

- Learn common toxicities for traditional chemotherapy and targeted therapy
- Describe how to monitor patients for chemotherapy-related toxicities
- Identify techniques used to prevent and mitigate common toxicities

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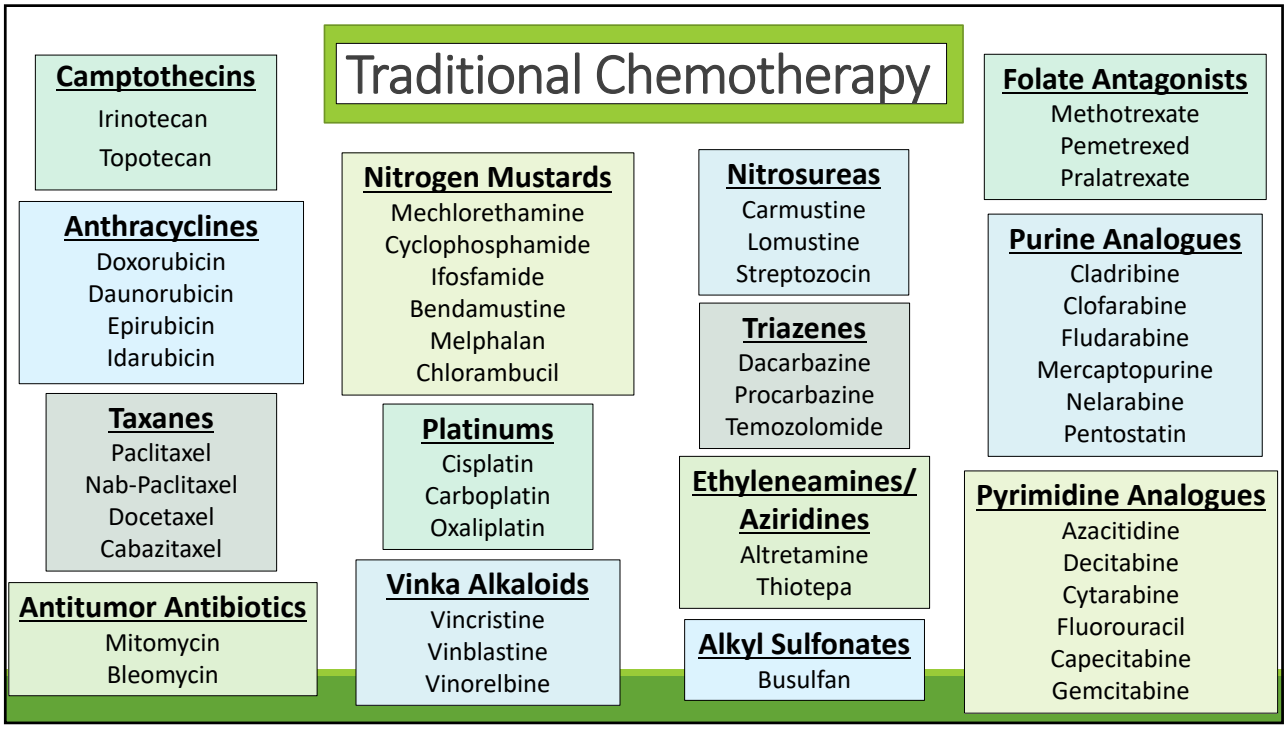

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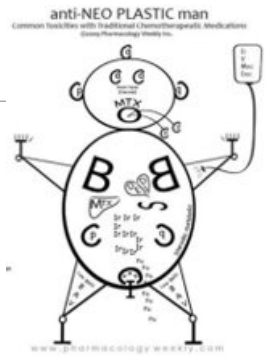

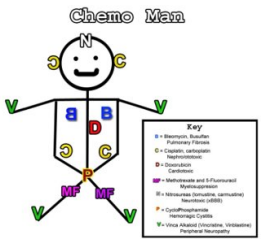

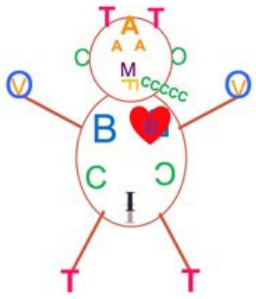

Chemo Man

COMMON TOXICITIES

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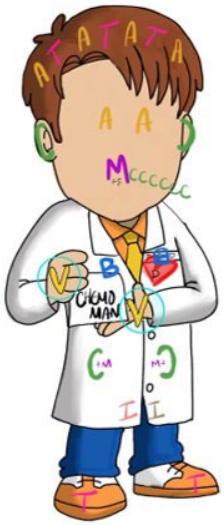

Traditional Chemotherapy Toxicity

- Severity varies greatly from person to person
  - Schedule and dose
  - Patient factors (eg, organ function, treatment history)
  - Disease
  - Concomitant medications
- Chemotherapy regimens usually combine drugs with different toxicity profiles
- Normal cells most likely to be damaged by chemo:
  - Blood-forming cells in the bone marrow
  - Hair follicles
  - Cells in the mouth, digestive tract, and reproductive system

Chemotherapy Side Effects | American Cancer Society

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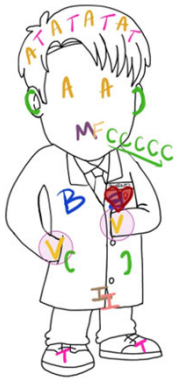
Camptothecins
Irinotecan
Topotecan

Camptothecins

Mechanism of Action: Inhibit topoisomerase I, stabilizing the cleavable complex, causing single strand DNA breaks



Irinotecan

- Commonly used for colorectal cancer (FOLFIRI)
- Early and late diarrhea
  - Early stage (within 24 hours) → Treat with atropine 0.25-1 mg subQ/IV
  - Late stage (~3-10 days after chemo) → Treat with loperamide 4 mg with first loose bowel movement then 2 mg after each loose stool (max 16 mg/day)

Monitor and replace electrolytes

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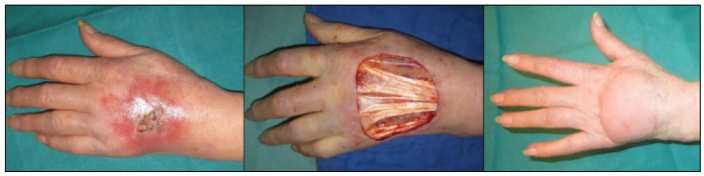
Anthracyclines
Doxorubicin
Daunorubicin
Epirubicin
Idarubicin

Anthracyclines

Mechanism of action: Inhibit topoisomerase II, preventing re-ligation of DNA and strand breaks. Form oxygen free radicals that add to cytotoxicity and toxicity.

Doxorubicin and daunorubicin

- Red-orange urine
- Mucositis
- Diarrhea
- Potent vesicants
  - Dexrazoxane for antidote
  - Administer ice to areas of extravasation



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Anthracyclines

Cardiotoxicity

- Cause: Myocardial cell injury
- Risk greatly increases after 400 mg/m2 of doxorubicin
  - Dexrazoxane – iron-chelating agent that inhibits cardiotoxic effects
  - Should not be combined with other agents that cause cardiotoxicity (eg, trastuzumab)
- If not diagnosed early, can lead to symptomatic heart failure
  - Prophylaxis and treatment with ACE inhibitors (eg, lisinopril) and beta blockers (eg, metoprolol)
  - Monitoring: Baseline ejection fraction (EF) required then repeat monitoring periodically

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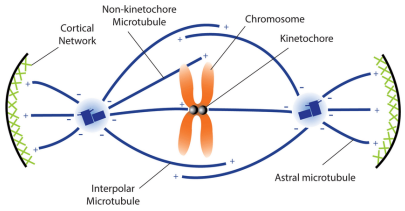
Microtubule Destabilizing Agents

Taxanes

Mechanism of action: Stimulate microtubule formation

Taxanes
Paclitaxel
Nab-Paclitaxel
Docetaxel
Cabazitaxel



Vinca Alkaloids

Mechanism of action: Inhibit microtubule formation

Vinka Alkaloids
Vincristine
Vinblastine
Vinorelbine

End result = Suppression of microtubule and mitotic spindle activity inhibits mitosis

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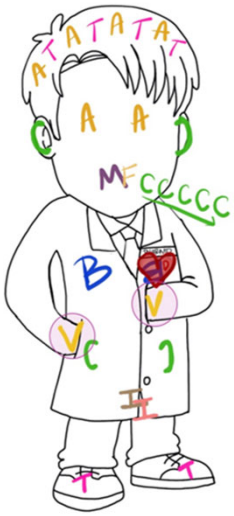
Taxanes

Paclitaxel and docetaxel

- Alopecia
  - Complete hair loss
  - Cold caps
- Hypersensitivity reactions
  - Paclitaxel
    - Cremophor
    - Pre-med with dexamethasone, diphenhydramine, famotidine
  - Docetaxel
    - Tween80
    - Pre-med with dexamethasone for 3 consecutive days, starting one day prior to docetaxel



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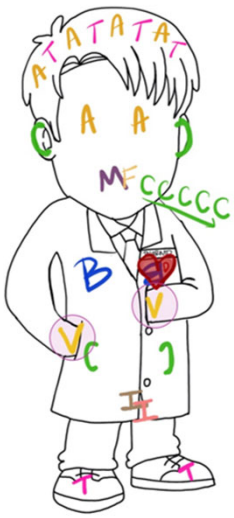
Taxanes

- Chemotherapy-induced peripheral neuropathy (CIPN)
  - Numbness, tingling, and/or pain in fingers & toes
  - Risk increases with cumulative dose and certain preexisting medical conditions
    - *Encourage patient reporting*
  - Management: Delay dose, dose reduce, or switch agents; consider duloxetine
- Taxane-associated pain syndrome (TAPS)
  - Myalgia or arthralgia symptoms within 24-48 hours of taxane administration that may last up to 7 days
  - Management: Gabapentin, duloxetine, ibuprofen, corticosteroids



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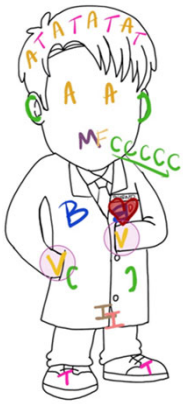
Vinca Alkaloids



Vincristine

- Potent vesicant
  - Hyaluronidase for antidote – increases distribution and absorption of locally injected extravasated substances
  - Use **warm compress** for extravasation
- Fatal if given intrathecally – should be prepared in an IV bag (not syringe)
- Vincristine-induced neuropathy
  - Sensory: Numbness, tingling
  - Motor weakness: Altered gait, impaired balance
  - Autonomic: Constipation

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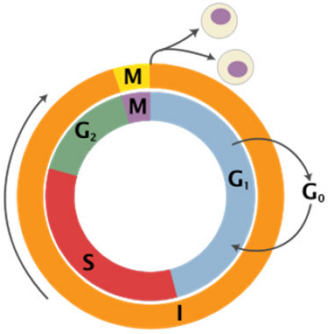
Antimetabolites

Mechanism of action: Damage cell DNA by either competing for enzyme binding sites or inserting directly into DNA or RNA strands



Folate Antagonists
Methotrexate
Pemetrexed
Pralatrexate

Purine Analogues
Cladribine
Clofarabine
Fludarabine
Mercaptopurine
Nelarabine
Pentostatin

Pyrimidine Analogues
Azacitidine
Decitabine
Cytarabine
Fluorouracil
Capecitabine
Gemcitabine

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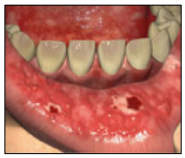
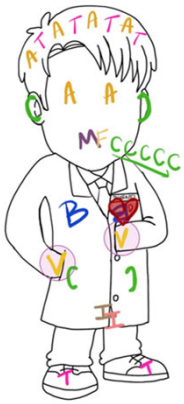
Folate Antagonists



Folate Antagonists
Methotrexate
Pemetrexed
Pralatrexate



- Mucositis
  - Pemetrexed and pralatrexate
    - Folic acid and Vitamin B-12 supplements – can reduce incidence of myelosuppression and mucositis
      - Start 1 week prior to treatment, take throughout therapy, and continue until 21 days after the last dose
  - Methotrexate
    - Do not supplement with folic acid
- Rash
  - Pemetrexed – pre-med with dexamethasone starting day prior to therapy

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Folate Antagonists

High-dose Methotrexate (>500-1000 mg/m2)

- Leucovorin rescue
  - Allows DNA synthesis to begin again, preventing toxicity (eg, myelosuppression, mucositis, and hepatotoxicity)
  - Start leucovorin 24 to 36 hours after start of methotrexate
- Alkalinization of urine & continuous hydration
  - Keep urine pH ≥7
  - Methotrexate is 6-10 times more soluble in alkaline urine – prevents crystallization in renal tubule
  - Frequent urine pH checks
  - Avoid excess use of diuretics

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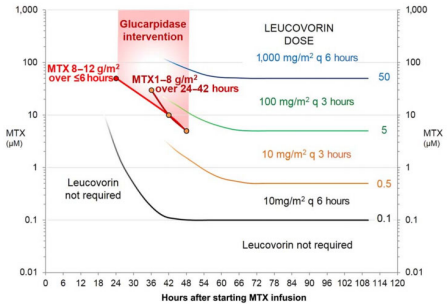
Folate Antagonists

High-dose Methotrexate (>500-1000 mg/m2)

- Avoid drug interactions
- Methotrexate levels
  - Drawn at 24, 36, and 48 hours after methotrexate infusion starts
  - Use methotrexate levels to ensure patient receiving adequate dose of leucovorin
  - Glucarpidase – antidote used to convert methotrexate into non-toxic metabolites
    - Administered when methotrexate levels and renal function elevated
    - Medical emergency

Drug Class	Example Agents
NSAIDs	Aspirin, salicylates, ibuprofen, ketorolac
Antibiotics	Penicillins, probenecid, ciprofloxacin, doxycycline
	Sulfonamides, tetracyclines
	Aminoglycosides, amphotericin
PPIs	Omeprazole, pantoprazole
Anti-seizure Agents	Phenytoin, carbamazepine
Certain Vitamins	Folic acid, ascorbic acid, MVI



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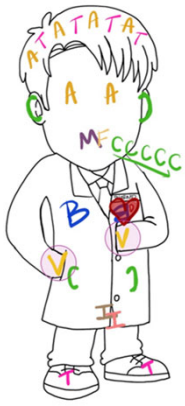
Pyrimidine Analogues

Pyrimidine Analogues

Azacitidine
Decitabine
Cytarabine
Fluorouracil
Capecitabine
Gemcitabine



Fluorouracil (5FU)

- Administration
  - Infusion
  - Bolus – leucovorin helps to improve 5FU efficacy
- Toxicity
  - Hand-foot syndrome
  - Diarrhea
  - Neutropenia & thrombocytopenia: 5FU bolus
  - Mucositis – oral cryotherapy (30 mins) during 5FU bolus

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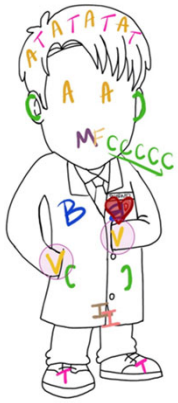
Pyrimidine Analogues

Cytarabine (AraC)

- High-dose cytarabine (>1000 mg/m2) can diffuse into tears and cross the blood-brain-barrier
  - Requires steroid eye drops to prevent chemical conjunctivitis
    - Prednisolone: 2 drops in each eye every 6 hours starting
  - Frequent neuro checks during therapy



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Alklylating Agents

Mechanism of action: Form highly reactive carbonium ion intermediates that bind to nucleophilic sites on DNA

- Cell kill results from DNA strand breaks, DNA mispairing, and inhibition of DNA replication & transcription

- Common class toxicities
  - Myelosuppression
  - Mucositis
  - Nausea & vomiting
  - Alopecia
  - Secondary leukemias

Nitrogen Mustards
Mechlorethamine
Cyclophosphamide
Ifosfamide
Bendamustine
Melphalan
Chlorambucil

Nitrosureas
Carmustine
Lomustine
Streptozocin

Triazenes
Dacarbazine
Procarbazine
Temozolomide

Platinums
Cisplatin
Carboplatin
Oxaliplatin

Ethyleneamines/ Aziridines
Altretamine
Thiotepa

Alkyl Sulfonates
Busulfan

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Nitrogen Mustards

Nitrogen Mustards
Mechlorethamine
Cyclophosphamide
Ifosfamide
Bendamustine
Melphalan
Chlorambucil

- Hemorrhagic cystitis
  - Caused by acrolein byproduct
  - Mesna – binds to an inactivates acrolein byproduct
    - Must be given with ifosfamide
    - Recommended for cyclorphosphamide doses >1000 mg/m2

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Platinums

Platinums
Cisplatin
Carboplatin
Oxaliplatin

- **Cisplatin**
  - Nephrotoxicity
  - Ototoxicity
  - Electrolyte wasting
  - Nausea & vomiting – acute and delayed
- **Carboplatin**
  - Increased risk of hypersensitivity reactions after ~6-8 doses
  - Calvert formula – accounts for renal function and ability to clear carboplatin
    - Dose = AUC x (CrCL + 25)
- **Oxaliplatin**
  - Neuropathy symptoms exaggerated by cold

Cisplatin = "Puke-platin"

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Platinums

Chemotherapy-induced nausea & vomiting (CINV)

- Definitions
  - Acute (0-24 hours after chemo)
  - Delayed (>24 hours after chemo)
  - Anticipatory (conditioned response from previous chemo treatment
- Risk factors
  - Female gender
  - Younger age
  - H/o motion or morning sickness

- Prophylaxis w/ multiple agents (3-4 if highly emetogenic)
  - Fosaprepitant
  - Dexamethasone
  - Palonsetron
  - Olanzapine

Cisplatin = "Puke-platin"

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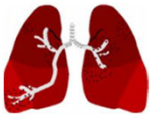
Antitumor Antibiotics

Antitumor Antibiotics
Mitomycin
Bleomycin

Mechanism of action: Cytotoxic effects result from the generation of activate oxygen radicals, leading to single- and double-strand DNA breaks

- Bleomycin
  - Pulmonary toxicity
    - Manifests as interstitial pneumonitis or pulmonary fibrosis
    - Risk increases when cumulative dose >400 units
    - Monitor
      - PFTs
      - Baseline DLCO & vital capacity
      - Chest x-ray



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Chemo Man Summary

Irinotecan
- Diarrhea

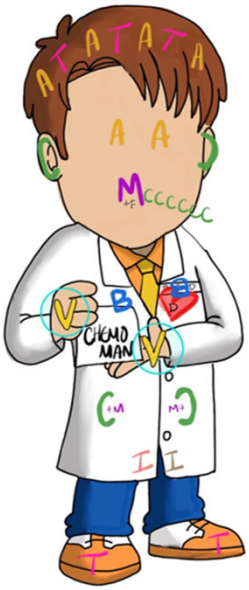
Doxorubicin
- Cardiotoxicity

Taxane (paclitaxel & docetaxel)
- Peripheral neuropathy
- Alopecia

Vincristine
- Peripheral neuropathy

Methotrexate
- Mucositis
- Nephrotoxicity

Ara-C (cytarabine)
- Neurotoxicity
- Ocular Toxicity



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Chemo Man Summary

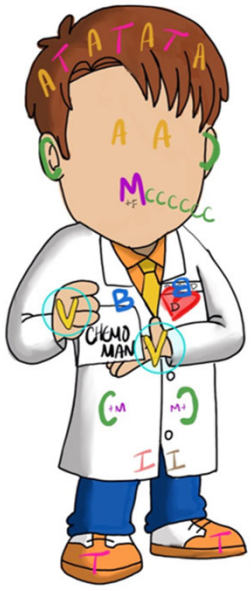
Fluorouracil
- Mucositis

Ifosfamide
- Hemorrhagic Cystitis

Cisplatin
- Ototoxicity
- Nausea/Vomiting
- Nephrotoxicity

Oxaliplatin
- Cold-Induced Neuropathy

Bleomycin
- Pulmonary Toxicity



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Targeted Agents

CAR-T Agents
Tisagenlecleucel
Axicabtagene ciloleucel
Lisocabtagene maraleucel
Brexucabtagene autoleucel
Ciltacabtagene autoleucel
Idecabtagene vicleucel

VEGF Inhibitors
Bevacizumab
Ramucirumab
Ziv-aflibercept

BiTE Therapy
Blinatumomab
Teclistamab

B-Cell Targeting Agents
Rituximab
Obinutuzumab
Tafasitamab
Daratumumab
Polatuzumab vedotin
Loncastuximab tesirine
Inotuzumab ozogamicin

HER-2 Inhibitors
Trastuzumab
Pertuzumab
Ado-trastuzumab emtansine
Trastuzumab deruxtecan

EGFR Inhibitors
Panitumumab
Cetuximab

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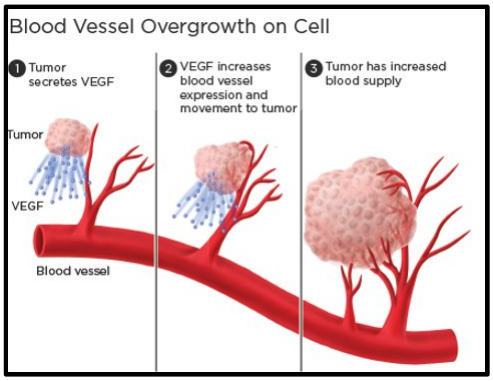
VEGF Inhibitors

VEGF Inhibitors
Bevacizumab
Ramucirumab
Ziv-aflibercept

Mechanism of action: Inhibition of vascular endothelial growth factor (VEGF) prevents the formation of new blood vessels (angiogenesis) and reduces tumor growth

- Bevacizumab
  - Hypertension
  - Proteinuria
  - Bleeding



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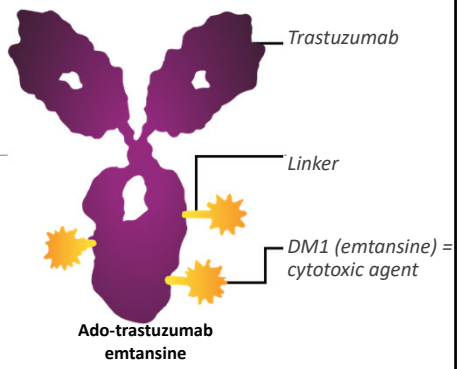
HER2 Inhibitors

Mechanism of action: Inhibits HER2 intracellular signaling pathways, which leads to apoptosis; HER2 is sometimes overexpressed in breast, gastric, endometrial, and colorectal cancers

- Toxicity
  - Cardiotoxicity - baseline EF then repeat every 3 months while on therapy
  - Infusion-related reactions
  - Diarrhea (pertuzumab)
- Pearls
  - Loading dose (pertuzumab, trastuzumab)
  - Pertuzumab not used alone
  - Antibody-drug conjugates
    - Ado-trastuzumab emtansine – linked to microtubule agent
    - Fam-trastuzumab deruxtecan – linked to topoisomerase inhibitor



HER-2 Inhibitors
Trastuzumab
Pertuzumab
Ado-trastuzumab emtansine
Fam-trastuzumab deruxtecan

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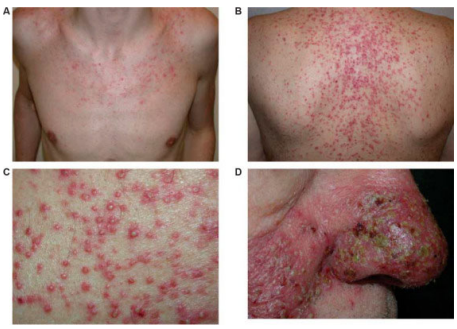
EGFR Inhibitors

EGFR Inhibitors
Panitumumab
Cetuximab

Mechanism of action: Inhibits epithelial growth factor receptor (EGFR), which leads to decreased cell proliferation and subsequent apoptosis

- Toxicity
  - Acne-like rash
    - Severity may be a marker of efficacy
    - Can use topical steroids or oral antibiotics (eg, minocycline) to prevent/treat
  - Infusion-related reactions



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B-Cell Targeting Agents

B-Cell Targeting Agents
Rituximab
Obinutuzumab
Tafasitamab
Daratumumab
Polatuzumab vedotin
Loncastuximab tesirine
Inotuzumab ozogamicin

Mechanism of action: Inhibits target antigen on B-cells, leading to apoptosis (CD20, CD19, CD22, CD79b)

- Toxicity
  - Infusion-related reactions
  - Increased risk of infections
    - Reactivation of Hepatitis B
    - Decreased response to vaccines

- Pearls
  - Titrate infusion (rituximab, obinutuzumab, daratumumab IV)
  - Antibody-drug conjugates
    - Polatuzumab vedotin– linked to microtubule agent
    - Loncastuximab – linked to alkylating agent
    - Inotuzumab – linked to antitumor antibiotics

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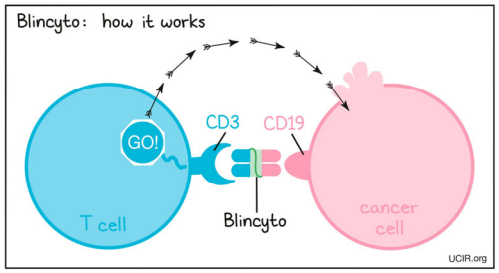
BiTE Therapy

BiTE Therapy
Blinatumomab
Teclistamab

Mechanism of action: Bispecific T-cell engager (BiTE) which binds to CD19 expressed on B-cells and CD3 expressed on T-cells, bringing them in close proximity and mediating the cytotoxic activity of T cells

- Blinatumomab
  - Must administer dexamethasone pre-medication
    - Prior to start of infusion
    - Prior to each dose increase
    - Each time dose held for ≥4 hours
  - Continuous infusion (28 days on → 14 days off)



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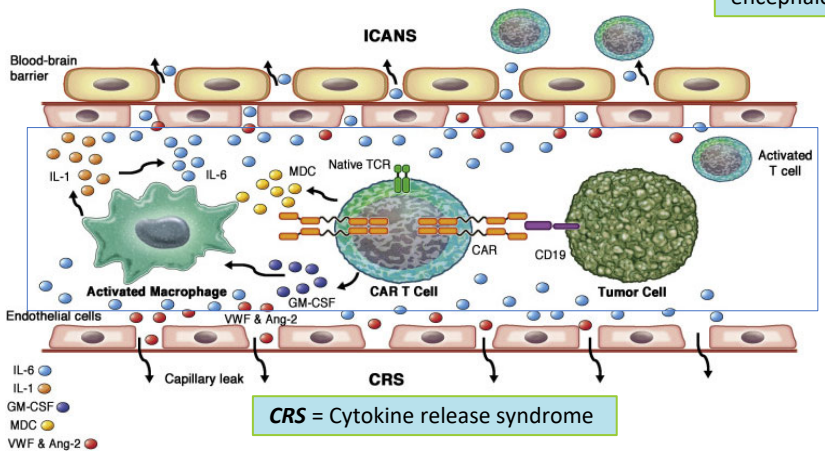
Toxicity

ICANS = Immune effector cell-associated encephalopathy syndrome



CRS = Cytokine release syndrome

- Potentially life-threatening inflammatory disorders
  - Result of T-cell activation, release of cytokines, and T-cell proliferation
- Mainstay of Treatment
  - CRS: tocilizumab, steroids
  - ICANS: steroids

June C, et al. *Science*. 2018; 359(6382): 1361-65
Gust J, et al. *Cancer Discov*. 2017 Dec;7(12):1404-1419
Freyer C et al. 2020;144(1):940-48

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CRS & ICANS

CYTOKINE RELEASE SYNDROME (CRS)

- Manifestations: fever, hypotension, hypoxia
- Typical onset: 2-5 days
- Typical duration: 7-8 days
- Serious events: organ dysfunction, capillary leak syndrome, atrial fibrillation

ICANS (NEUROTOXICITY)

- Manifestations: headache, tremor, dysgraphia, altered mental status
- Typical onset: 4-10 days
- Typical duration: 14-17 days
- Serious events: seizure, cerebral edema

CAN OVERLAP

Slide credit: HOPA
June C, et al. *Science*. 2018; 359(6382): 1361-65
Lee DW et al. Biol Blood Marrow Transplant. 2019;25:625-638

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ICANS Grading System

ICE Score Grading	
Score (points)	**Parameter**
4	Orientation: year, month, city, hospital
3	Naming: ability to name 3 objects (eg, point to clock, pen, button"
1	Following commands: ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")
1	Writing: ability to write a standard sentence (eg, "the quick brown fox jumps over the lazy dog")
1	Attention: ability to count backwards from 100 by 10

ASTCT ICANS Consensus Grading for Adults				
Neurotoxicity Domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE Score	7-9	3-6	0-2	0 (patient unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous tactile stimuli to arouse
Seizure	N/A	N/A	Any clinical seizure (focal, generalized, or nonconvulsive) that resolves with intervention	Life-threatening prolonged seizure (> 5 min) or repetitive seizures without return to baseline
Motor findings	N/A	N/A	N/A	Deep focal motor weakness
Elevated ICP/ Cerebral Edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve palsy; or papilledema; or Cushing's triad

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CRS Grading System

ASTCT CRS Consensus Grading	
Grade 1	- Fever (≥ 38°C) with or without constitutional symptoms (ie. myalgia, arthralgia, and malaise) - No hypoxia or hypotension present
Grade 2	- Fever[ε] (≥ 38°C) with hypotension not requiring vasopressors AND/OR - Hypoxia requiring the use of oxygen via low flow nasal canula (≤ 6 L/min)
Grade 3	- Fever[ε] (≥ 38°C) with hypotension requiring 1 vasopressor (with or without vasopressin) AND/OR - Hypoxia requiring high flow nasal cannula (> 6 L/min), facemask, nonrebreather mask, or venturi mask
Grade 4	- Fever[ε] (≥ 38°C) with hypotension + multiple vasopressors (excluding vasopressin) AND/OR - Hypoxia requiring positive pressure (ie. CPAP, BiPAP, mechanical ventilation, and intubation)

RN Expectations

- Document ICE score, as well as grade of CRS and ICANS in nursing note once per shift
- Obtain baseline handwriting sample

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Managing CRS & ICANS

- Grade 1: Continue blinatumomab and administer supportive care
- Grade 2: Pause blinatumomab immediately and administer supportive care
- Grade 3-4: Stop blinatumomab immediately and administer supportive care
  - Dexamethasone 8 mg IV/PO every 8 hours for up to 3 days (tapered over 4 days)
  - Consider tocilizumab 8 mg/kg (max 800 mg) for severe or life-threatening CRS
    - DO NOT USE FOR ICANS (does not cross blood brain barrier)
- Grade 4 or >1 seizure: Discontinue blinatumomab permanently

If blinatumomab infusion paused for ≥4 hours, dexamethasone must be redosed prior to restarting infusion. Provider decision to restart blinatumomab based on patient clinical status.

*Of note, the PI gives different guidance for when to pause blinatumomab infusion – at Abbott, we are choosing to pause the infusion at grade 2 (with the hopes that earlier provider assessment of CRS/ICANS will lead to prevention of worse complications)

Lee DW. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.
Amgen. Blincyto (blinatumomab) [package insert].Revised February 2022.

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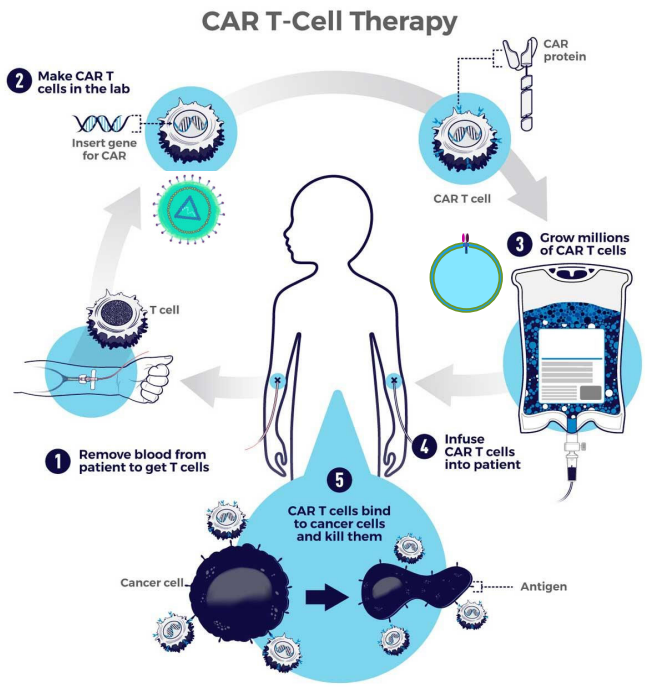

CAR-T Process

1. Remove blood from patient to get T-cells
2. Make CAR-T cells in the lab
3. Grow millions of CAR-T cells
4. Infuse CAR-T cells into patient
5. CAR-T cells bind to cancer cells and kill them

CAR-T Agents
Tisagenlecleucel
Axicabtagene ciloleucel
Lisocabtagene maraleucel
Brexucabtagene autoleucel
Ciltacabtagene autoleucel
Idecabtagene vicleucel

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Questions?

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