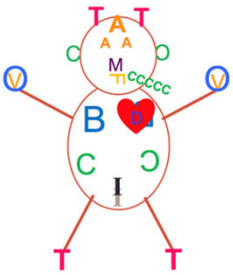
Toxicity of Traditional Chemotherapy & Targeted Therapy



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October 3rd, 2023

AllinaHealth | ABBOTT NORTHWESTERN HOSPITAL

Special thanks to Des Hanna, PharmD, BCPS for custom chemo man

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Disclosure

The presenters have 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 treatment-related toxicities
- Identify techniques used to prevent and mitigate common toxicities

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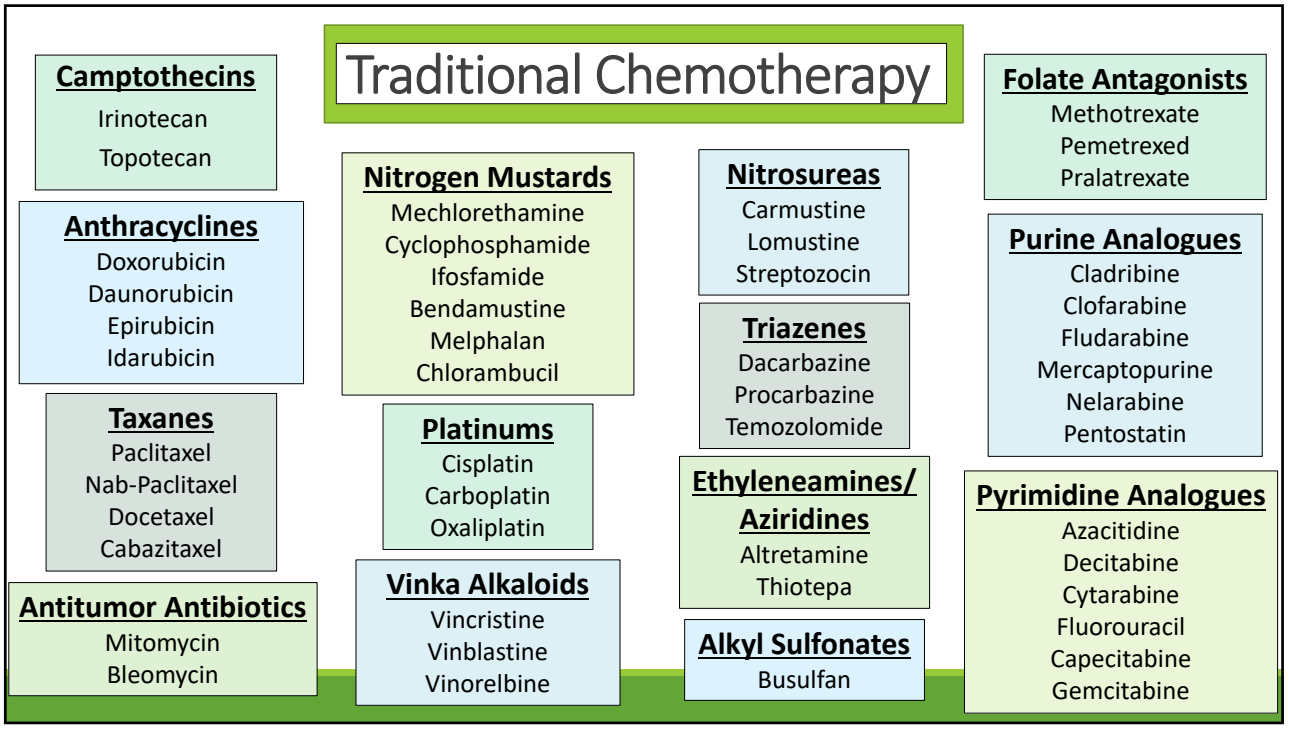

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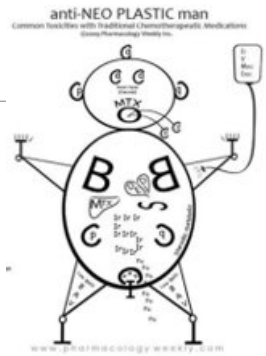

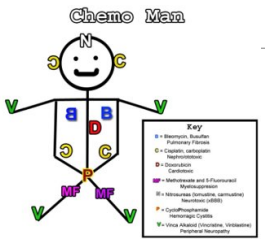

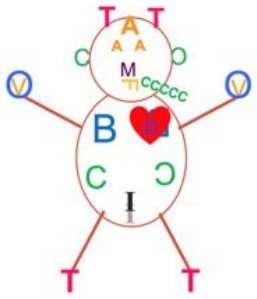

Chemo Man

COMMON TOXICITIES

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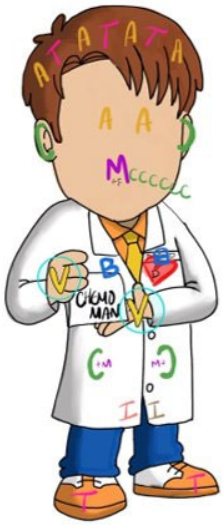

Traditional Chemotherapy Toxicity

- 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

Camptothecins
Irinotecan
Topotecan

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 at onset of diarrhea then 2 mg every 2 hours as need (or 4 mg every 4 hours overnight) until cessation of diarrhea for 12 hours. Limit to 48 hours of treatment.

Monitor and replace electrolytes!!!

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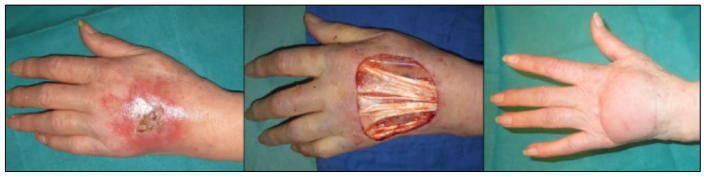
Anthracyclines

Anthracyclines
Doxorubicin
Daunorubicin
Epirubicin
Idarubicin

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 ~450 mg/m2 of doxorubicin
  - Dexrazoxane – inhibits cardiotoxic effects
  - Avoid combination with other cardiotoxic agents (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

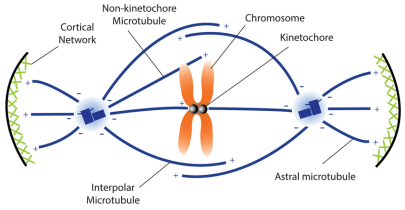
Taxanes

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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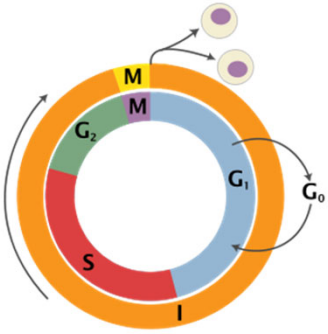
Antimetabolites

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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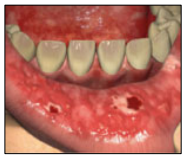
Folate Antagonists



Folate Antagonists
Methotrexate
Pemetrexed
Pralatrexate

- Mucositis
  - Pemetrexed
    - 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/m^2)

- 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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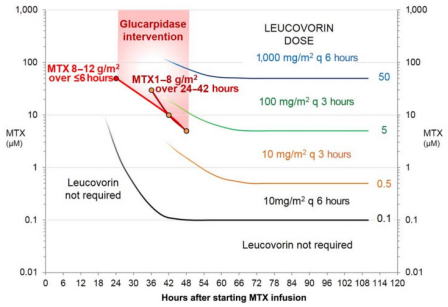
Folate Antagonists

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

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

- Avoid drug interactions
- Methotrexate levels
  - Drawn at various intervals, beginning 24 hours after methotrexate infusion BEGINS
  - 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!



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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/m^2) 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 prior to start of high-dose cytarabine → Continue for 48-72 hours after cytarabine complete
  - Frequent neuro checks during therapy
    - Neurotoxicity can manifest acute cerebellar toxicity, personality changes, or may be severe (eg, seizure/coma)

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Alkylating 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

Ifosfamide and cyclophosphamide

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

Nitrogen Mustards
Mechlorethamine
Cyclophosphamide
Ifosfamide
Bendamustine
Melphalan
Chlorambucil

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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

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Platinums

Chemotherapy-induced nausea & vomiting

- 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
  - History of motion or morning sickness
- Anti-emetic Prophylaxis
  - Examples: Fosaprepitant, dexamethasone, palonsetron, olanzapine
  - May require multiple agents for adequate anti-nausea control (especially if highly emetogenic chemotherapy

Cisplatin = "Puke-platin"

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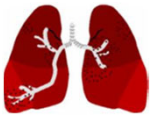
Antitumor Antibiotics

Antitumor Antibiotics
Mitomycin
Bleomycin

Mechanism of action: Cytotoxic effects result from the generation of activated 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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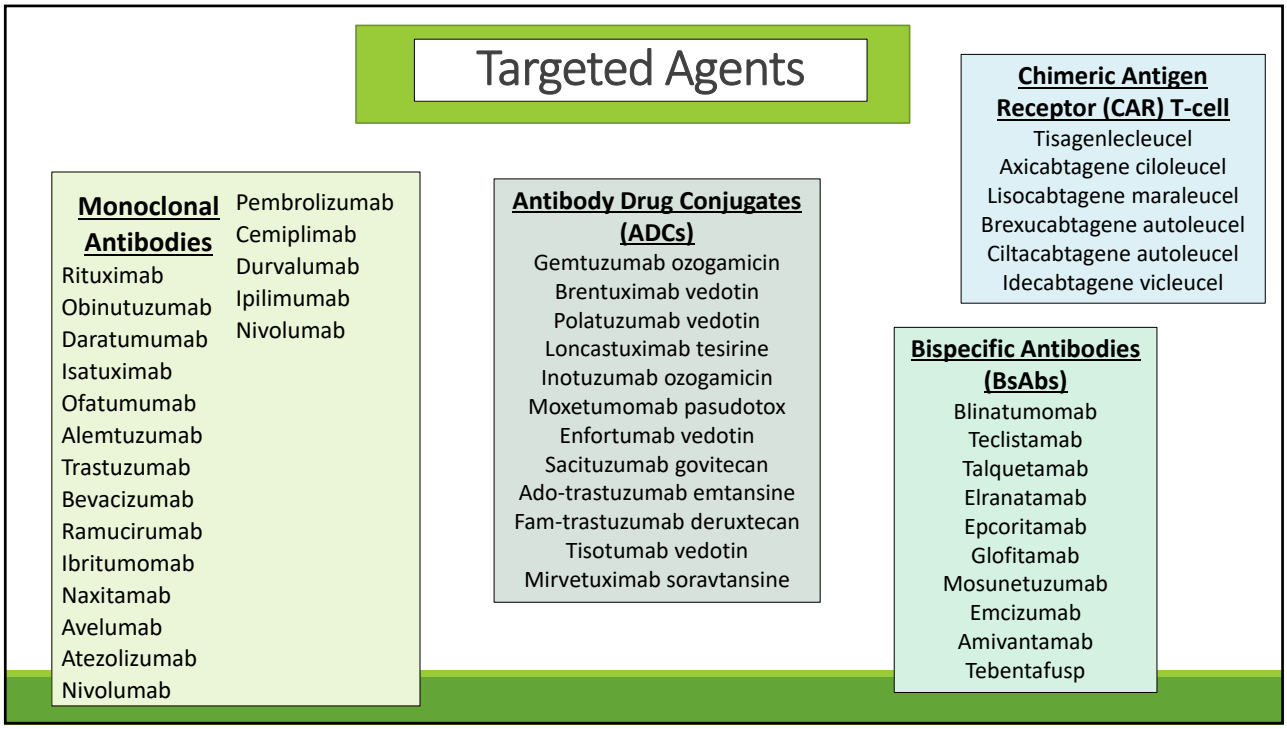

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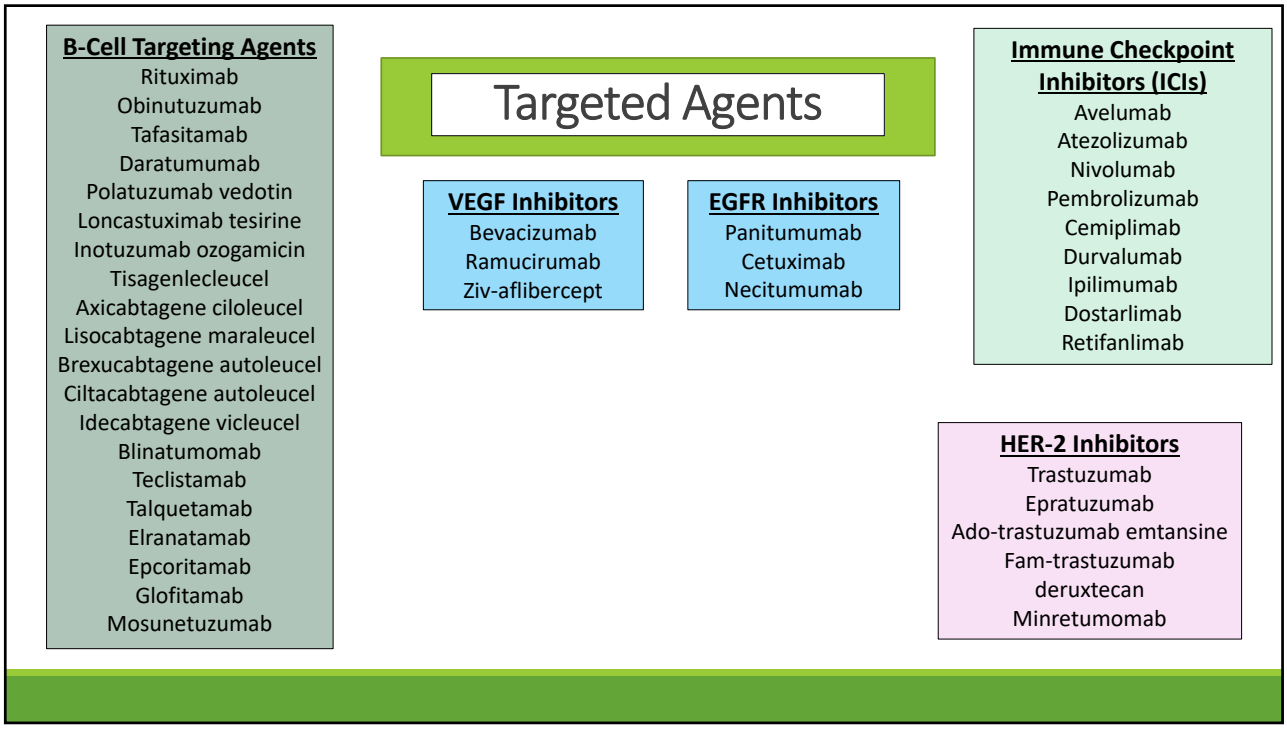

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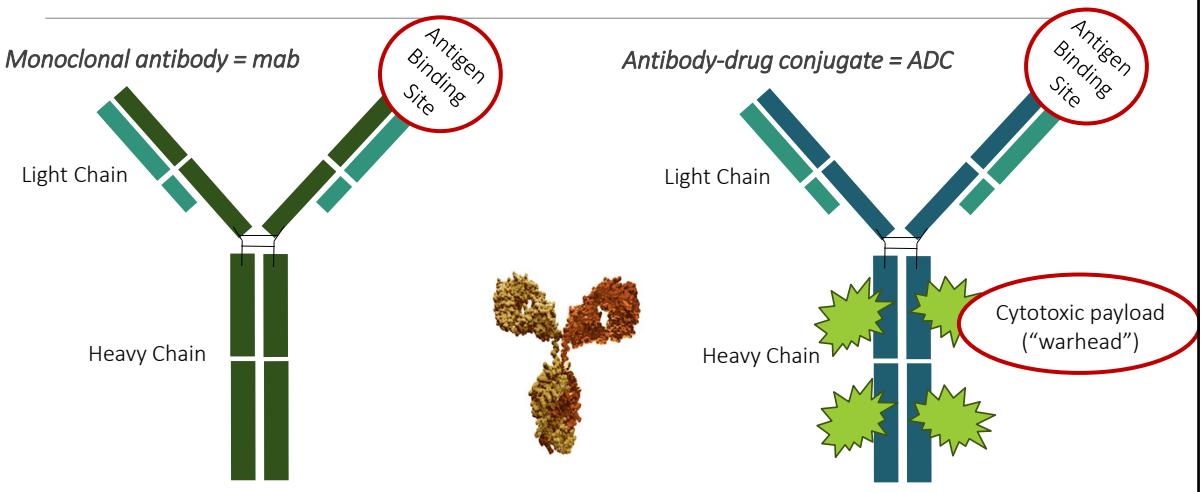
Using Immunoglobulins as Cancer Therapy



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VEGF Inhibitors

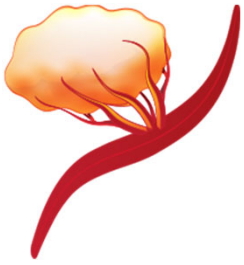
VEGF Inhibitors
Bevacizumab
Ramucirumab

Mechanism of action: Inhibits vascular endothelial growth factor (VEGF), preventing the formation of new blood vessels (angiogenesis), reducing tumor growth

Target = VEGF

Toxicity

- Hypertension – caution if SBP/DBP > 160/90
- Proteinuria - caution if urine protein ≥2+ (100-299 mg/L) on 2 occurrences
- Bleeding – increased risk of hemorrhage
  - Hold prior to elective surgery and following major surgery



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HER2 Inhibitors

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

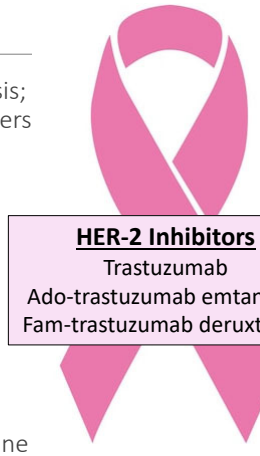
Target = HER2

Toxicity

- Cardiotoxicity – monitor EF while on therapy
- Diarrhea (pertuzumab)

Pearls

- Pertuzumab should not be used as monotherapy
- Loading dose (eg, pertuzumab, trastuzumab)
- ADC cytotoxic payload: Peripheral neuropathy with ado-trastuzumab emtansine
- SubQ formulations (eg, trastuzumab, trastuzumab/pertuzumab)



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

Breastcancer.org

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EGFR Inhibitors

EGFR Inhibitors
Panitumumab
Cetuximab
Amivantamab

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

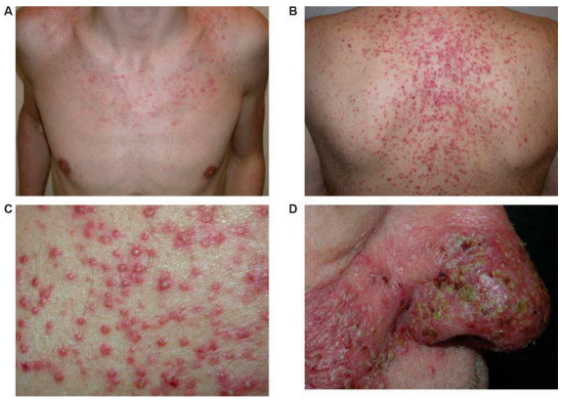
Target = EGFR

Toxicity:

- Acne-like rash: Severity may be a mark of efficacy
  - Treatment: Topical steroids or oral antibiotics (eg, minocycline)
- Paronychia – treatment with topical antibiotics or steroids

Pearl

- Amivantamab - bispecific antibody that targets both EGFR and MET
  - High rate of infusion-related reactions



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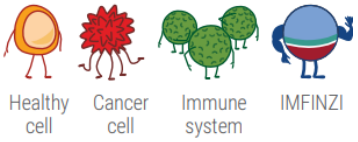
Immune Checkpoint Inhibitors

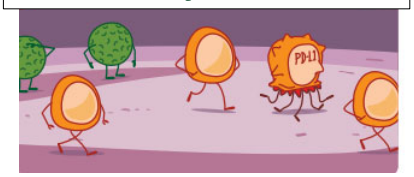


Mechanism of action: Inhibit checkpoint proteins from binding with their partner proteins, preventing the "off" signal from being sent, allowing T-cells to kill cancer cells

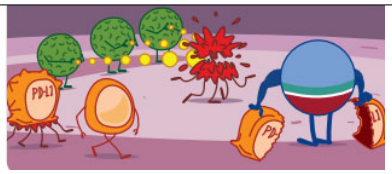
Targets = PD-1, PD-L1, CTLA4

Immune Checkpoint Inhibitors (ICIs)
Nivolumab (PD-1)
Pembrolizumab (PD-1)
Durvalumab (PD-L1)
Ipilimumab (CTLA4)

Immune System Evasion



Recognition & Destruction



Immune Checkpoint Inhibitors - NCI (cancer.gov)

Immunotherapy for BTC, uHCC, NSCLC & ES-SCLC – IMFINZI® (durvalumab)

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Checkpoint Inhibitors

L^2 E G S

Immune Checkpoint Inhibitors (ICIs)
Nivolumab (PD-1)
Pembrolizumab (PD-1)
Durvalumab (PD-L1)
Ipilimumab (CTLA4)

Treat a variety of cancer types

- Breast, bladder, cervical, endometrial, colon/stomach/rectal
- Liver, head and neck, renal cell, melanoma, Hodgkin lymphoma

Toxicity: Immune-related adverse effects (irAE)

- **Liver/Lungs:** hepatotoxicity; **Endocrine:** hypothyroidism, **GI**: diarrhea/colitis, **Skin:** maculopapular rash/pruritis
- Other: pneumonitis, headache, acute kidney injury, myocarditis, any
- Grade irAEs using CTCAE (Common Terminology Criteria for Adverse Events)

Immune Checkpoint Inhibitors - NCI (cancer.gov)

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Checkpoint Inhibitors

Pearls

- Ipilimumab should not be used as monotherapy
- Use cautiously in patients with immune-mediated disease (eg, rheumatoid arthritis, multiple sclerosis) – ICIs may cause disease flare
- Risk vs benefit in patients taking concomitant steroids (prednisone equivalent >10 mg)
- Multinational Association of Supportive Care in Cancer (MASCC) – recommend risk vs benefit discussion around concurrent use with cannabis due to potential for decreased efficacy of checkpoint inhibitors

Harms

We recommend against the use of cannabinoids for any indication in cancer patients undergoing treatment with a checkpoint inhibitor.

Level of evidence – III; Grade of evidence – C; Category of guideline – Suggestion

Immune Checkpoint Inhibitors - NCI (cancer.gov)

MASCC Guidelines - MASCC

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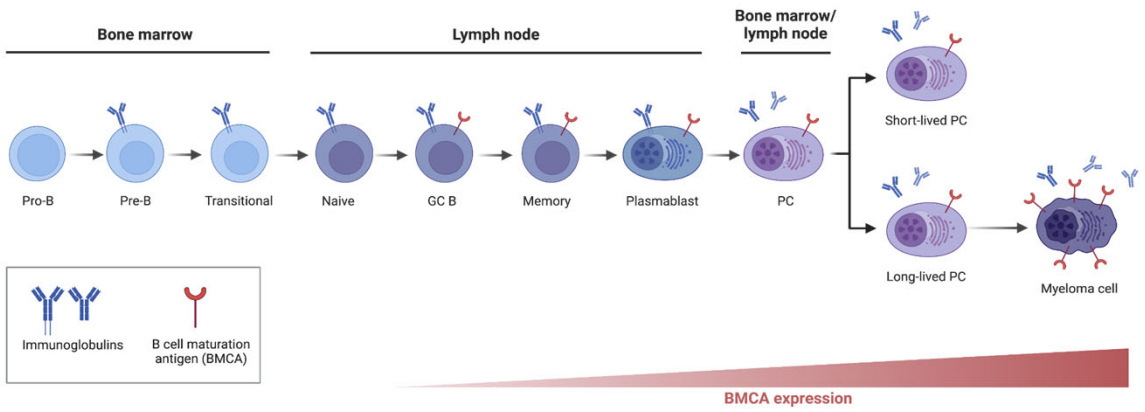

Targeting B-Cells

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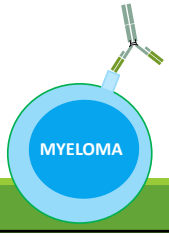
B-Cell Targeting Agents

CD20
Rituximab
Obinutuzumab
Ofatumumab
Loncastuximab tesirine
Epcoritamab
Glofitamab
Mosunetuzumab

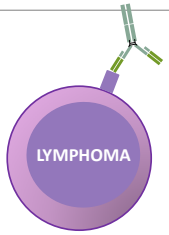
CD19
Tafasitamab
Blinatumomab
Tisagenlecleucel
Axicabtagene ciloleucel
Lisocabtagene maraleucel
Brexucabtagene autoleucel



CD38
Daratumumab
Isatuximab

SLAMF7
Elotuzumab

BCMA
~~Belantamab mafodotin~~
Ciltacabtagene autoleucel
Idecabtagene vicleucel
Teclistamab
Elranatamab

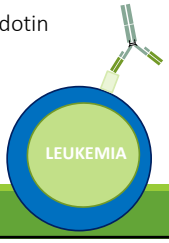


GPRC5D
Talquetamab

CD79b
Polatuzumab vedotin

CD22
Inotuzumab ozogamicin

CD30
Brentuximab vedotin



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B-Cell Targeting Agents

Mechanism of action: Bind to target antigen expressed on B-cells, activating complement-dependent B-cell cytotoxicity and antibody-dependent cellular cytotoxicity

Toxicity
- ADC cytotoxic payload: Peripheral neuropathy with polatuzumab vedotin, veno-occlusive disease (VOD) with inotuzumab ozogamicin
- Infusion-related or hypersensitivity reactions (eg, rituximab, ~~daratumumab IV~~)
- Increased risk of infections
  - Pancytopenia
  - Reactivation of Hepatitis B
  - Decreased response to vaccines

Pearl:
- SubQ formulation available: rituximab, daratumumab

Monoclonal antibodies & ADCs
Rituximab
Obinutuzumab
Tafasitamab
Daratumumab
Polatuzumab vedotin
Loncastuximab tesirine
Inotuzumab ozogamicin

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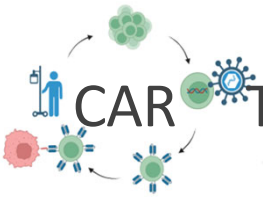


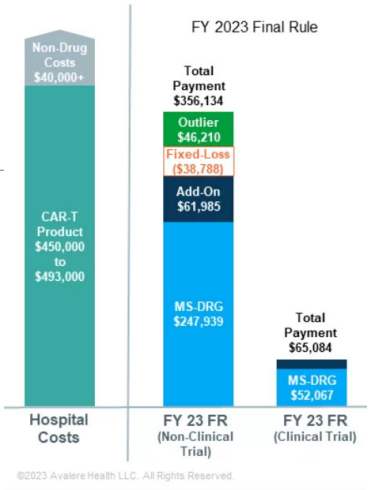
CAR T-Cell Therapy

Mechanism of action: engineered chimeric antigen receptor (CAR) T-cells help orchestrate the immune response; CARs recognize and bind to specific proteins (antigens) on the surface of cancer cells, leading to cell death (apoptosis)

Multiple Myeloma: Target = BCMA

Lymphoma, ALL: Target = CD19

Toxicity
- CRS/ICANS
- Financial Toxicity: ~$450-493k
- Pancytopenia
- Hypogammaglobulinemia → IVIG



Currently Available CAR T

Tisagenlecleucel = Tisa-cel (Kymriah®) – DLBCL, FL, ALL
Axicabtagene ciloleucel = Axi-cel (Yescarta®) – DLBCL, FL
Lisocabtagene maraleucel = Liso-cel (Breyanzi®)– DLBCL, FL
Brexucabtagene autoleucel = Brexu-cel (Tecartus®)– MCL, ALL
Ciltacabtagene autoleucel = Cilta-cel (Carvykti®)– multiple myeloma
Idecabtagene vicleucel = Ide-cel (Abecma®) – multiple myeloma

CAR T Cells: Engineering Immune Cells to Treat Cancer - NCI

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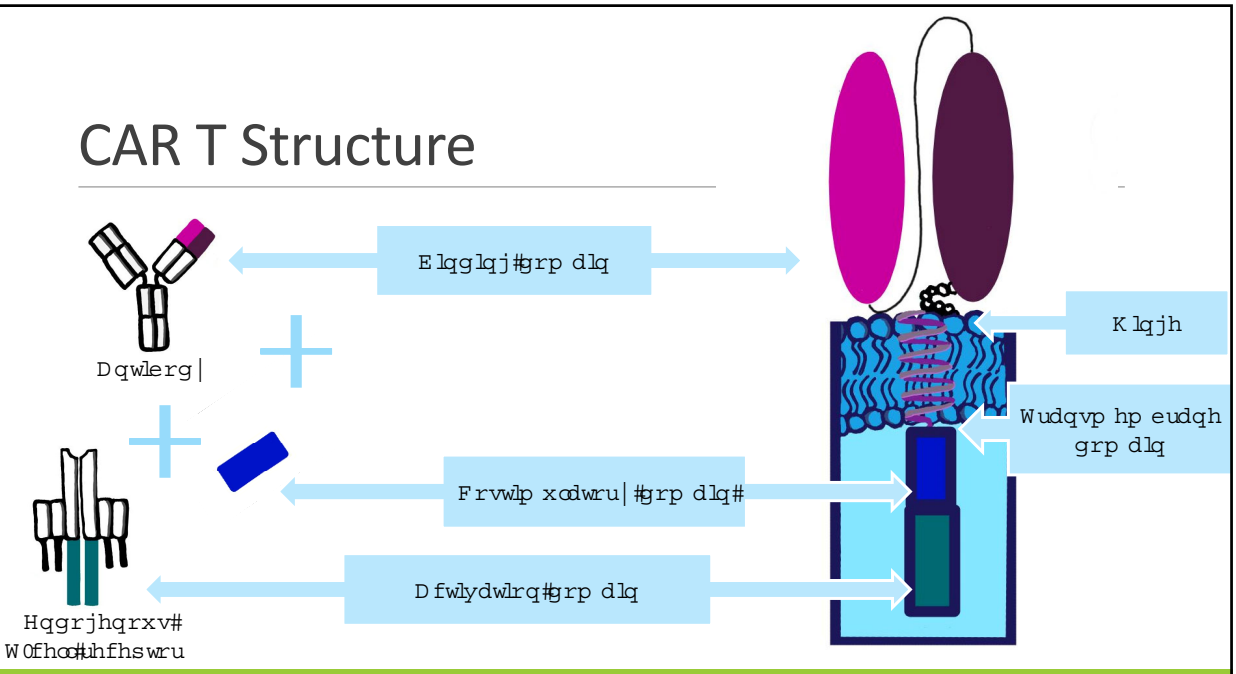
CAR T Structure



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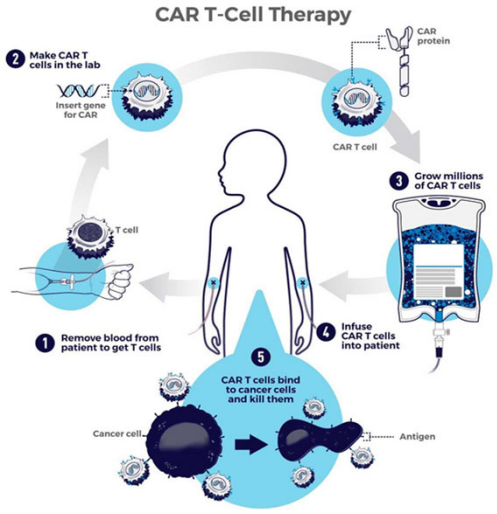
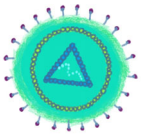
Chimeric Antigen Receptor (CAR) T-Cell Therapy



Process:

1. Remove blood from patient to retrieve own (autologous) T-cells
2. Make CAR T-cells in lab
3. Grow millions of CAR T-cells
4. Infuse CAR T-cells into patient
5. CAR T-cells bind to antigen on cancer cells and kill them



CAR T-cell Therapy Infographic. National Institute of Health. Accessed Sept 13, 2023. www.cancer.gov/about-cancer/treatment/research/car-t-cell-therapy-infographic

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Bispecific Antibody Therapy

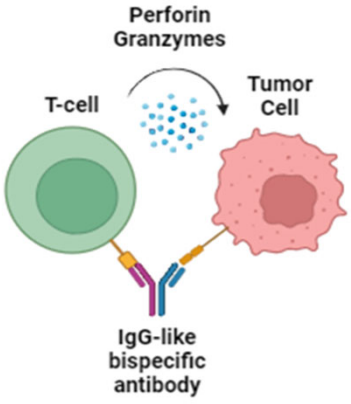
Mechanism of action: Bind to target antigen expressed on B-cells and CD3 expressed on T-cells, bringing them in close proximity and mediating the cytotoxic activity of T cells

Multiple Myeloma: Targets = BCMA, GPRC5D

Lymphoma: Target = CD20

Toxicity

- CRS/ICANS
- Financial Toxicity: $25-50k per month ($285-650k total)
- Infection: Pancytopenia & hypogammaglobulinemia
- Tumor flare



Currently Available Heme Bispecifics

Blinatumomab (Blincyto®) – B-ALL
Epcoritamab (Epikinly®) – DLBCL
Glofitamab (Columvi®) – DLBCL
Teclistamab (Tecvayli®) – multiple myeloma
Talquetamab (Talvey®) – multiple myeloma
Elranatamab (Elrexfio®) – multiple myeloma
Mosunetuzumab (Lunsumio®) – FL

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Comparison Between Bispecifics

Indications: ALL, multiple myeloma, DLBCL, follicular lymphoma	Different target antigens (BCMA, GPRC5D, CD19, CD20)	Pre-medications	Fixed duration vs. ongoing
Unique toxicities	Step-up dosing +/- hospitalization	REMS program requirements (multiple myeloma)	Different routes of administration (subQ, IV)

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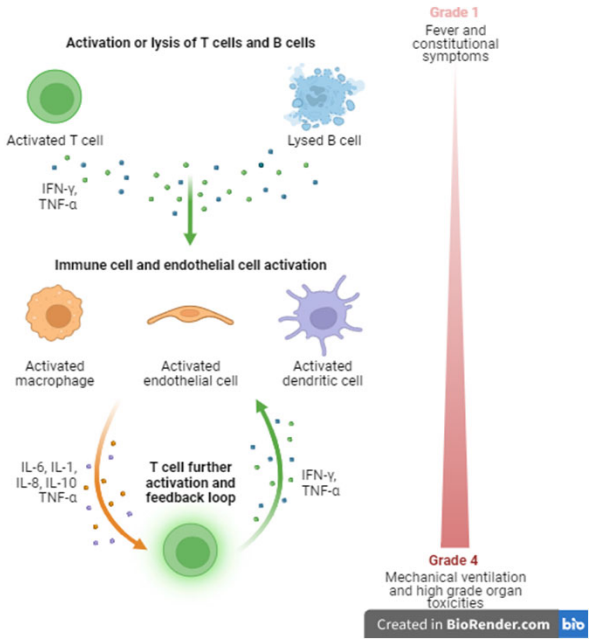

CRS/ICANS

Cytokine release syndrome (CRS)

- Manifestations: fever, hypotension, hypoxia
- Serious events: organ dysfunction, capillary leak syndrome, atrial fibrillation
- Treatment: tocilizumab, steroids*

Immune effector cell-associated encephalopathy syndrome (ICANS)

- Manifestations: headache, tremor, dysgraphia, altered mental status
- Serious events: seizure, cerebral edema
- Treatment: steroids*

*For refractory CRS/ICANS, can consider anakinra or other agent

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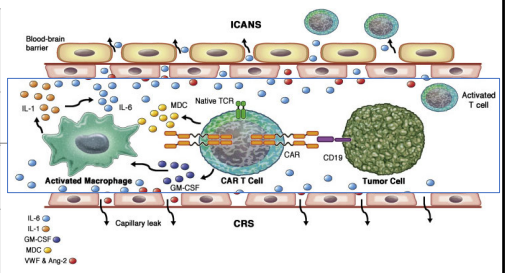
ASTCT Consensus Grading of CRS

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	≥ 38 ℃	≥ 38 ℃	≥ 38 ℃	≥ 38 ℃
With Hypotension	None	No vasopressor	Vasopressor +/- vasopressin	Multiple vasopressors (excluding vasopressin)
And/or Hypoxia	None	Low flow nasal cannula	High-flow nasal cannula, facemask, non-rebreather, Venturi mask	Positive pressure (CPAP, bipap, mechanical ventilation)

£ In patients who have CRS then receive antipyretic or anticytokine therapy, fever is no longer required to grade subsequent CRS severity (CRS grading then driven by hypotension and/or hypoxia)



CRS Grading

RN expectations: Obtain ICE score, as well as grade of CRS and ICANS in nursing note once per shift and prior to each dose

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Managing CRS for Bispecifics

General Principles

- Administer aggressive supportive care
- Wait until CRS resolves prior to administering next bispecific dose
- Consider treating as next higher grade:
  - If clinical status worsens or does not improve within 24 hours
  - If patient frail or elderly
- Monitor cardiac, renal, and hepatic function closely
- Avoid growth factors during CRS risk
- For recurrent grade 3 or any grade 4 CRS, discontinue agent permanently

CRS	Pharmacologic	Supportive
Grade 1	Consider dexamethasone 10 mg (PO/IV)	• Treat fever and neutropenia if present, monitor fluid balance, and administer antipyretics & analgesics as needed • IV fluids, vasopressors, & oxygen as needed
Grade 2-3	Dexamethasone 10-20 mg PO/IV every 6 hours • If no improvement in 4 hours, consider tocilizumab 8 mg/kg (max 800 mg)	
Grade 4	Methylprednisolone 1000 mg IV daily	

Consider anakinra for refractory ICANS - if used, add levofloxacin and anti-mold coverage due to increased risk of infections

Does not include blinatumomab

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ICE Score (points)	Parameter
4	Orientation: year, month, city, hospital (1 point for each)
3	Naming: ability to name 3 objects (eg, point to clock, pen, button" -1 point for each)
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 the same simple sentence (eg, "the quick brown fox jumps over the lazy dog")
1	Attention: ability to count backwards from 100 by 10

ICANS Grading

RN expectations: Obtain ICE score, as well as grade of CRS and ICANS in nursing note once per shift and prior to each dose

ASTCT Consensus ICANS Grading

Neurotoxicity	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score (10 – Grade 0)	7-9	3-6	0-2	0
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Stupor or coma
Seizure	N/A	N/A	Clinical seizure resolves rapidly	Prolonged seizure
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness
Elevated ICP	N/A	N/A	Focal or local edema	Diffuse cerebral edema

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Managing ICANS for Bispecifics

General Principles

- Administer aggressive supportive care
- Wait until ICANS resolves prior to administering next bispecific dose
- Low threshold to initiate levetiracetam
- Consider treating as next higher grade:
  - If clinical status worsens or does not improve within 24 hours
  - If patient frail or elderly
- Consider neurologic consult for grade ≥3 ICANS
- For recurrent grade 3, grade ≥3 seizure, or any grade 4 ICANS, discontinue agent permanently

CRS	Pharmacologic	Supportive
Grade 1	• Consider dexamethasone 10 mg (PO/IV) • Consider levetiracetam 500 mg (PO/IV) for seizure prophylaxis	• Treat fever and neutropenia if present, monitor fluid balance, and administer antipyretics & analgesics as needed • IV fluids, vasopressors, & oxygen as needed
Grade 2-3	Dexamethasone 10-20 mg PO/IV every 6 hours	
Grade 4	Methylprednisolone 1000 mg IV daily	

Consider anakinra for refractory ICANS - if used, add levofloxacin and anti-mold coverage due to increased risk of infections

Does not include blinatumomab

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Managing CRS/ICANS for Blinatumomab

- **Grade 1:** Continue blinatumomab and administer supportive care
- **Grade 2:** Pause blinatumomab immediately and administer supportive care
- **Grade 3-4:** Pause blinatumomab immediately and administer supportive care
  - Dexamethasone 8 mg IV/PO every 8 hours for up to 3 days (tapered quickly)
  - Consider tocilizumab 8 mg/kg (max 800 mg) for severe or life-threatening CRS
    - Do NOT use tocilizumab for isolated 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**
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)

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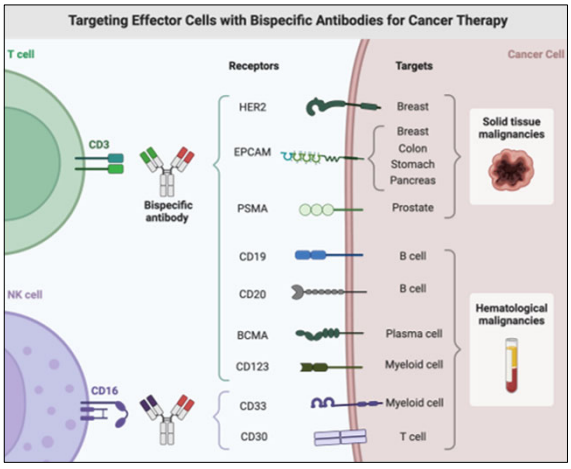

Future Directions

- Use various constructs & target antigens in multiple cancers
  - Tarlatamab – lung cancer bispecific in clinical trials; target = DLL-3
- Move bispecifics from inpatient to outpatient infusion clinic
  - Minimize financial toxicity (AllinaForward)
  - Increase revenue
- Learn how to sequence these agents & manage toxicity

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Summary of Targeted Agents

- Most agents have the potential to cause an infusion-related or hypersensitivity reaction
- Target antigen determines toxicity
- Bispecifics. . .they're coming
  - Several bispecifics have come out in the last year – there are similarities and differences amongst all the products
  - All have risk for cytokine release syndrome (CRS) and neurotoxicity (ICANS), so be aware of how to recognize & manage toxicity (KNOW YOUR RESOURCES)

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FUN Bispecific Resources

- Oncology Nursing Society
  - **ONS Nursing Society Meeting:** Sarah Hayes, PharmD, BCOP & Justine Preedit, PharmD, BCOP presenting at the October 10th for the Oncology Nursing Society Meeting (Boludo – Downtown Minneapolis)
  - Podcast Episode 275: Bispecific Monoclonal Antibodies in Hematologic and Solid Tumors
  - Podcast Episode 176: Oncologic Emergencies 101: Cytokine Release Syndrome
- Research to Practice Podcast
  - Disease experts, including RN/APPs, discuss their experience with administering chemoimmunotherapy in large academic medical centers & ***how community hospitals can use lessons learned to successfully administer these complex agents to patients***
- WolverHeme Podcast
  - Two malignant heme pharmacists drink and nerd out about data
  - Podcast Episode 12: Tinder for T cells – Bispecifics in DLBCL

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Questions?

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