Monitoring Parameters for Chemotherapy and Immunotherapy

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Disclosure

- I have nothing to disclose. There are no relevant financial or personal relations with any ACCME defined commercial interests.

Objectives

- Identify chemotherapy and immunotherapy drug classes
- Recognize lab monitoring parameters prior to treatment initiation and during treatment
- Discuss the most common toxicities associated chemotherapy and immunotherapy
- Understand clinical strategies used to manage or reduce risk of potential toxicities

Chemotherapy

- Chemical agents utilized to inhibit the growth of malignant cells
  - Destroy cancer cells
  - Prevent further cancer cell replication
- Goals of chemotherapy
  - Curative: eliminate all cancer cells to attain a permanent cure
  - Adjuvant: supportive therapy post primary treatment to prevent recurrence
  - Neoadjuvant: therapy prior to primary treatment to reduce tumor size
  - Palliative: symptom management or slow disease progression

Chemotherapy Drug Classes

- **Alkylating agents**
  - Alkyl sulfonates
  - Aziridines
  - Nitrogen mustards
  - Nitrosoureas
  - Platinum agents
  - Triazenes/Methylating agents
- **Antimetabolites**
  - DNA hypomethylating agents
  - Folate antagonists
  - Pyrimidine analogs
  - Purine analogs
  - Miscellaneous: hydroxyurea
- **Antimicrotubular agents**
  - Epothilones
  - Halichondrin B analogs
  - Taxanes
  - Vinca alkaloids
- **Antitumor antibiotics**
  - Anthracyclines
  - Actinomycins
  - Miscellaneous: bleomycin, mitomycin, mitoxantrone
- **Topoisomerase inhibitors**
  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    - Anthracyclines

Chemotherapy Mechanism of Action

M Phase Specific

Antimicrotubule Agents

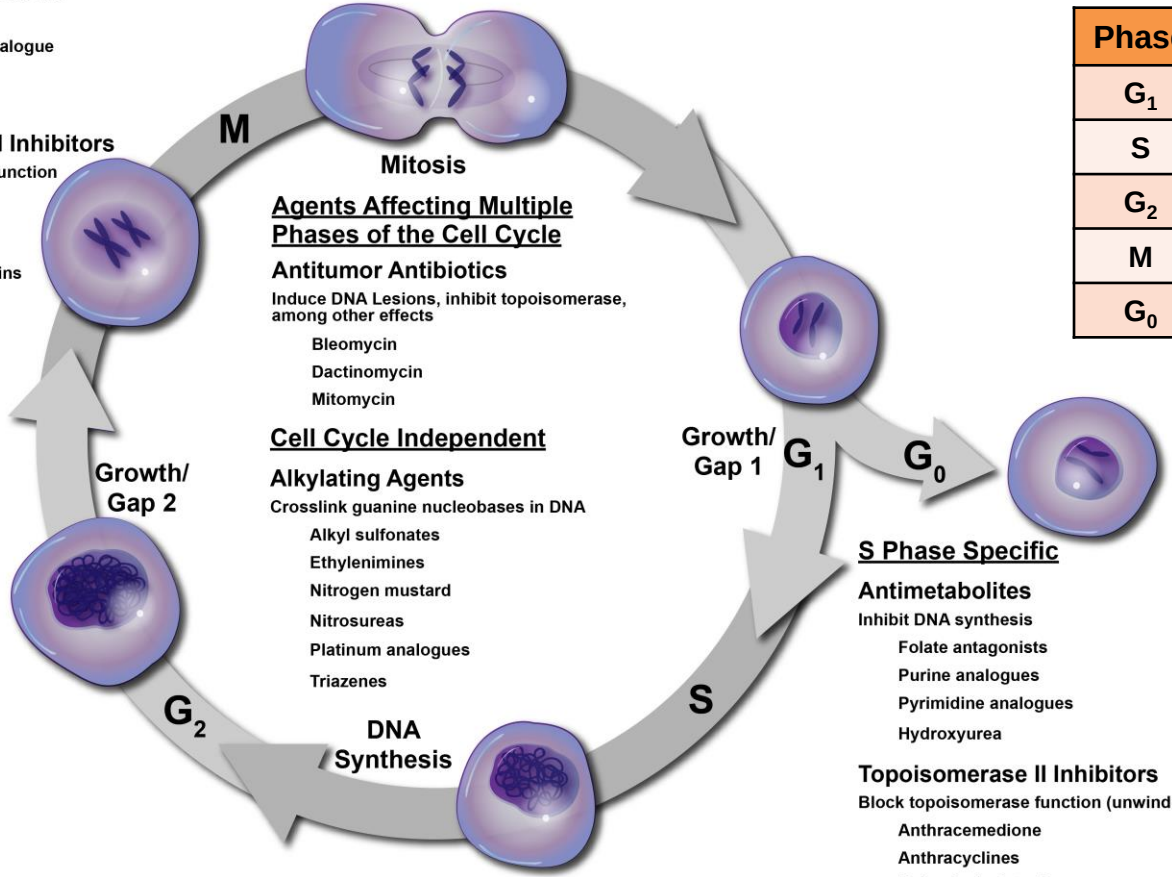
Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins



Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

Alkylating Agents

Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
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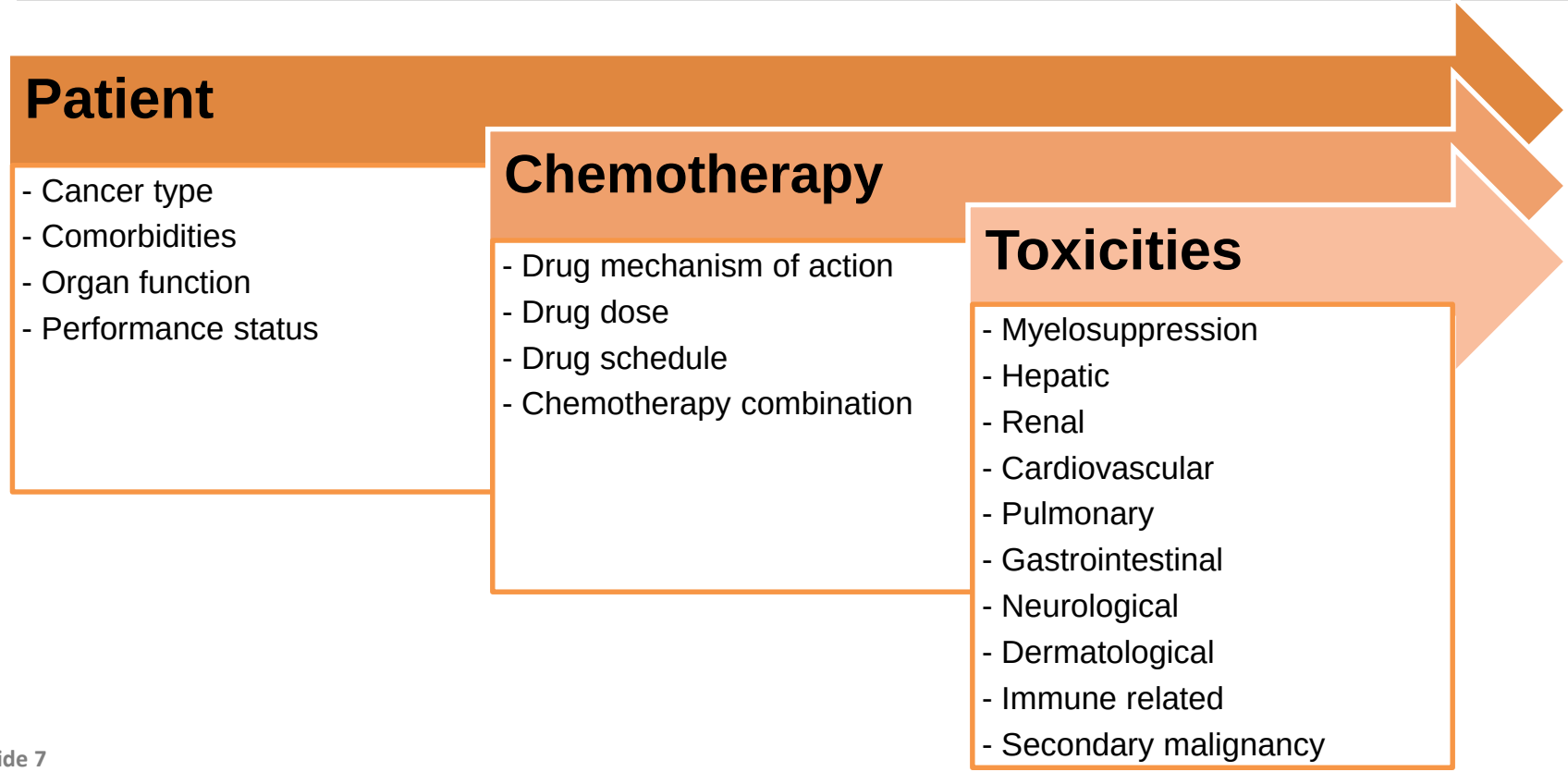
- Epipodophyllotoxins

Phase	Role
G_1	DNS synthesis preparation
S	DNA synthesis
G_2	Mitosis preparation
M	Mitosis and cell division
G_0	Resting state

Chemotherapy Toxicity Overview



Lab Monitoring Overview

- Complete blood count (CBC) with differential
  - Required prior to almost all chemotherapy orders
  - Evaluating absolute neutrophil count (ANC), hemoglobin, hematocrit, and platelets
- Liver function tests (LFTs)
- Serum creatinine (SCr)
- Left ventricular ejection fraction (LVEF)
- Pulmonary function tests (PFTs)
- Electrolytes
- Pregnancy test

LFT Monitoring for Chemotherapy

*Ado-trastuzumab (Kadcyla)**	Cytarabine (Ara-C)	Doxorubicin Liposomal (Doxil)	Irinotecan Liposomal (Onivyde)	Pemetrexed (Alimta)
Bendamustine (Treanda)	Dacarbazine (DTIC-Dome)	Epirubicin (Ellence)	Irinotecan (Camptosar)	Pralatrexate (Folotyn)
Bortezomib (Velcade)	Dactinomycin (Actinomycin-D)	Eribulin (Halaven)	Ixabepilone (Ixempra)	Streptozocin (Zanosar)#
*Brentuximab (Adcetris)**	Daunorubicin (Cerubidine)	Etoposide (Etopophos)	Methotrexate	Temsirolimus (Torisel)^
Cabazitaxel (Jevtana)*	Daunorubicin/Cytarabine (Vyxeos)*	Gemcitabine (Gemzar)	Mitomycin (Mutamycin)	Trabectedin (Yondelis)*
Carfilzomib (Kyprolis)	Decitabine (Dacogen)	*Gemtuzumab (Mylotarg)**	Mitoxantrone (Novantrone)	Vinblastine (Velban)
Clofarabine (Clolar)*	Docetaxel (Taxotere)*	Idarubicin (Idamycin)	Paclitaxel (Taxol)	Vincristine (Oncovin)
Cyclophosphamide (Cytoxan)	Doxorubicin (Adriamycin)	Ifosfamide (Ifex)	Paclitaxel Protein Bound (Abraxane)	Vinorelbine (Navelbine)

*** = with each dose**
^ = every other dose
 # = weekly

SCr Monitoring for Chemotherapy

Azacitadine (Vidaza)	Cisplatin (Platinol)*	Epirubicin (Ellence)	Methotrexate	Temsirolimus (Torisel)^
Bendamustine (Treanda)	Clofarabine (Clolar)*	Eribulin (Halaven)	Mitomycin (Mutamycin)	Topotecan (Hycamtin)
Bleomycin (Blenoxane)	Cyclophosphamide (Cytoxan)	Etoposide (Etopophos)	Oxaliplatin (Eloxatin)	Trabectedin (Yondelis)
*Brentuximab (Adcetris)**	Cytarabine (Ara-C)	Fludarabine (Fludara)	Pemetrexed (Alimta)*	
Carboplatin (Paraplatin)	Daunorubicin (Cerubidine)	Idarubicin (Idamycin)	Pentostatin (Nipent)*	
Carfilzomib (Kyprolis)	Daunorubicin/Cytarabine (Vyxeos)*	Gemcitabine (Gemzar)	Pralatrexate (Folotyn)	
Carmustine (BiNCU)	Decitabine (Dacogen)	Ifosfamide (Ifex)	Streptozocin (Zanosar)#	

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LVEF Monitoring for Chemotherapy

- Diagnostic procedures
  - Echocardiogram (ECHO)
  - Multigated acquisition (MUGA) scan
- Chemotherapy induced cardiotoxicity
  - Definition
    - Heart failure (HF) symptoms with ≥5% LVEF reduction to <55%
    - No HF symptoms with ≥10% LVEF reduction to <55%
  - Type 1
    - Cumulative dose related
    - Permanent damage
    - Ex. Anthracyclines
  - Type 2
    - Not cumulative dose related
    - Reversible damage
    - Ex. Trastuzumab

Ado-trastuzumab (Kadcyla)	Daunorubicin (Cerubidine)
Daunorubicin/Cytarabine (Vyxeos)	Doxorubicin (Adriamycin)
Doxorubicin Liposomal (Doxil)	Epirubicin (Ellence)
Idarubicin (Idamycin)	Mitomycin (Mutamycin)
Mitoxantrone (Novantrone)	Trabectedin (Yondelis)

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Maedica (Buchar). 2013 Mar;8(1):59-67.

PFT Monitoring for Chemotherapy

- Diagnostic procedures
  - Spirometry
    - Forced vital capacity (FVC)
    - Forced expiratory volume in 1 second (FEV_1)
  - Lung diffusing capacity
    - Diffusing capacity of the lung for carbon monoxide (D_{LCO})

Baseline and Periodic PFTs
Bleomycin (Blenoxane)
Carmustine (BiNCU)

Baseline Chest X-Ray
Bortezomib (Velcade)
Methotrexate
Temsirolimus (Torisel)

Consider Chest X-Ray and/or PFTs for new or worsening pulmonary symptoms	
Ado-trastuzumab (Kadcyla)	Methotrexate
Bortezomib (Velcade)	Mitomycin (Mutamycin)
Cyclophosphamide (Cytoxan)	Pemetrexed (Alimta)
Gemcitabine (Gemzar)	Temsirolimus (Torisel)
Irinotecan Liposomal (Onivyde)	Vinorelbine (Navelbine)
Irinotecan (Camptosar)	

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Semin Oncol. 2006 Feb;33(1):98-105.

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Alkylating Agents: Nitrogen Mustards

	Cyclophosphamide	Ifosfamide

Monitoring Parameters	• Myelosuppression **(DLT)**
	• Hemorrhagic cystitis
	  - Acrolein metabolite accumulation
	  - Prevention via mesna and hydration
	• Nephrotoxicity
	• Nausea and vomiting
	  - >1.5 g/m^2: high emetic risk
	  - ≤1.5 g/m^2: moderate emetic risk
	• Alopecia
	• Sterility
	• Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
		• Myelosuppression **(DLT)**
		• Hemorrhagic cystitis
		  - Acrolein metabolite accumulation
		  - Prevention via mesna and hydration
		• Nephrotoxicity
		• Nausea and vomiting
		  - ≥2 g/m^2: high emetic risk
		  - <2 g/m^2: moderate emetic risk
		• Alopecia
		• Sterility
		• Neurotoxicity
		  - Chloroacetaldehyde accumulation
		  - Consider methylene blue or thiamine treatment

DLT = Dose Limiting Toxicity

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Devita, Hellman, And Rosenberg's Cancer, 2009.

Alkylating Agents: Platinums

	Cisplatin	Carboplatin	Oxaliplatin
Nephrotoxicity	**+++ (DLT)**	**+**	**+**
	• Typically reversible • Pre and post IV hydration • Mannitol, K, and Mg • Urine output >100 mL/hr	• Calvert dosing equation: AUC x (GFR + 25)	• CrCl <30 ml/min may require dose reduction
Myelosuppression	**+**	**+++ (DLT)**	**++**
	• Primarily anemia	• Primarily thrombocytopenia • Delayed (nadir 3-6 weeks)	• Thrombocytopenia with higher doses • Mild anemia and neutropenia
Neurotoxicity	**+++**	**+**	**+++ (DLT)**
	• Reversible • Peripheral neuropathy is most common symptom • Cumulative dose >300 mg/m^2	• Peripheral neuropathy • Not common	• Acute: common, reversible, and exacerbated by cold • Delayed: irreversible, associated with cumulative dose • Pharyngolaryngeal dysesthesias

Devita, Hellman, And Rosenberg's Cancer, 2009. | Oncol Rev. 2014 Sep 23;8(2):256. | Oncologist. 2015 Apr;20(4):411-32.

Alkylating Agents: Platinums

	Cisplatin	Carboplatin	Oxaliplatin
Nausea and Vomiting	**+++**	**++**	**++**
	• High emetic risk • Acute and delayed (2-5 days post dose)	• AUC ≥4: High emetic risk • AUC <4: Moderate emetic risk	• Moderate emetic risk
Ototoxicity	**+++**	**+**	**+**
	• Typically irreversible • Cumulative dose >400 mg/m^2 • Ototoxic drug interactions		
Hypersensitivity	**-**	**+**	**+**
		• Potentially IgE mediated • Delayed reaction with increased risk with ≥6 cycles	• Mild: slow infusion rate and administer antihistamine and/or steroid • Severe: desensitization protocol

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Antimetabolites: Folate Antagonist

Methotrexate (MTX)

- Folate analog
  - Inhibits dihydrofolate reductase and thymidylate synthetase
  - Results in the cessation of DNA synthesis
- Multiple indications
  - Monotherapy
  - Component of several treatment regimens
- MTX toxicity risk factors
  - Dose
  - MTX serum levels
  - Pharmacokinetic variations
  - Pharmacogenomic variations
  - Third space fluid collections
  - Drug interactions

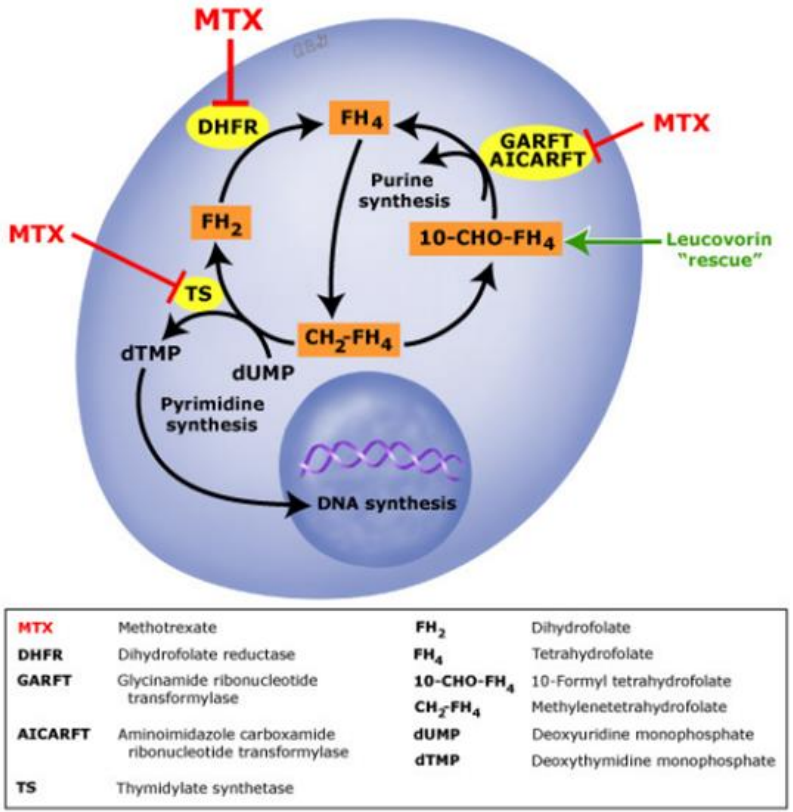


Image: LaCasce, AS. UpToDate, 2018.

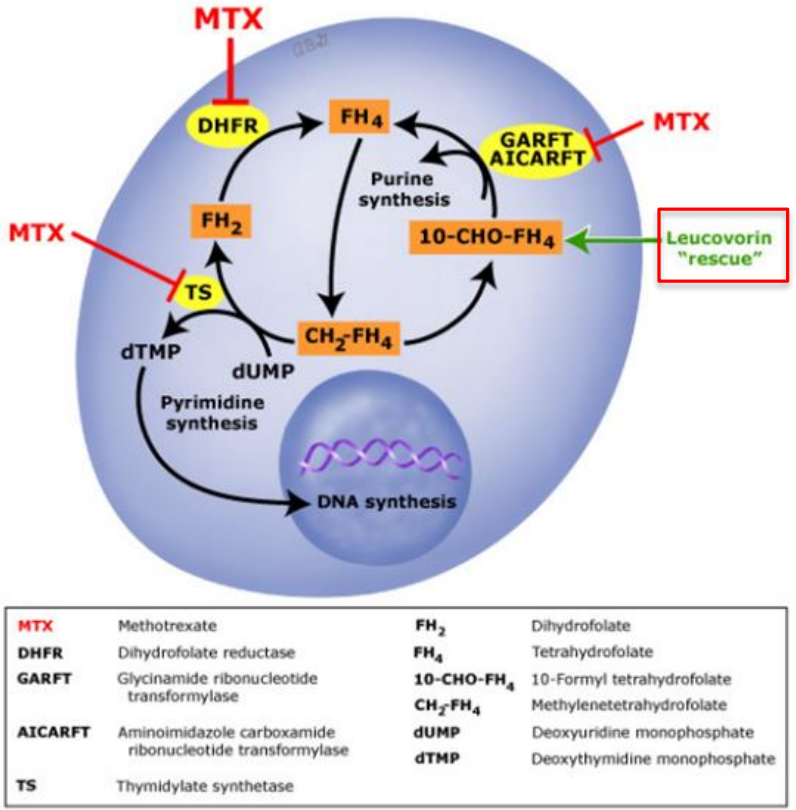
J Cancer Sci Ther 2013;5: 106-112. | Oncologist. 2016;21:1-12.

MTX Dose	Definition	General Indications	Toxicities
Low	< 50 mg/m^2	• Nonmalignant disorders	• Gastrointestinal (GI) • Central nervous system (CNS) • Alopecia • Stomatitis • Macular rash • Mild hepatotoxicity • Mild myelosuppression
Intermediate	50 – 500 mg/m^2	• Nonmalignant disorders • Malignant disorders	• Dose dependent toxicity • Generally no aggressive prophylaxis • Leucovorin rescue rarely needed at doses $\leq$ 250 mg/m^2
High (HDMTX)	$\geq$ 500 mg/m^2	• CNS prophylaxis • CNS lymphomas • Osteosarcomas • Leptomeningeal metastases	• Considered lethal dose • Renal dysfunction • Hepatic toxicity • Myelosuppression • Gastrointestinal (GI) mucositis • Requires aggressive prophylaxis and multiple leucovorin doses

J Cancer Sci Ther 2013;5: 106-112. | LaCasce, AS. UpToDate, 2018.

Leucovorin

- "Rescue" agent utilized in HDMTX regimens
  - Increases reduced cellular folate stores
  - Overcomes MTX inhibition of purine and pyrimidine synthesis
- Effective in the prevention of HDMTX toxicity
  - Nephrotoxicity
  - Myelosuppression
  - Neurotoxicity
  - Gastrointestinal toxicity
- Leucovorin rescue regimens vary
  - MTX dose and infusion duration
  - Chemotherapy indication
  - Institution specific protocols



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J Cancer Sci Ther 2013;5: 106-112. | J Drug Metab Toxicol 2012;3:125.

HDMTX Toxicity Monitoring

Nephrotoxicity	• Direct tubular injury via MTX precipitation and constriction of afferent arteriole • Typically reversible and recovery in 2-3 weeks • Risk factors: volume depletion, acidic urine, and drug interactions • Prevention: - IV hydration: 2.5-3.5 L/m^2/day of fluids 4-12 hours prior to MTX infusion and then continuing fluids for 24-48 hours or until discharge - Urine alkalinization: Urine pH $\geq$7 prior to MTX initiation with IV or oral sodium bicarbonate and maintain pH $\geq$7 until MTX serum levels <0.1 µM - Leucovorin rescue • Management: increase leucovorin dose and consider glucarpidase
Hepatotoxicity	• Idiosyncratic with recovery in 1-2 weeks • Risk factors: alcoholism, diabetes, obesity, and hepatitis B or C infection • Prevention: avoid hepatotoxic drugs, reduce risk, and leucovorin rescue
Pulmonary Toxicity	• Idiosyncratic reaction with low incidence (<1%) but potentially fatal • Usually occurs within 1st year of therapy • Folate repletion does not decrease risk • Management: hold MTX and provide supportive care +/- corticosteroids

J Cancer Sci Ther 2013;5: 106-112. | J Drug Metab Toxicol 2012;3:125. | Oncologist. 2007 Nov;12(11):1299-308.

HDMTX Toxicity Monitoring

Myelosuppression	• Pancytopenia with complete recovery around 3 weeks • Prevention: leucovorin rescue • Management: perform risk assessment to consider transfusions, granulocyte colony stimulating factor (G-CSF), and/or antibiotics
Neurologic Toxicity	• Acute encephalopathy: 12-72 hours after IV or IT MTX administration with presentation of somnolence, confusion, seizures, insomnia, or coma • Subacute encephalopathy: few weeks after MTX initiation with symptoms of paraplegia, cerebellar dysfunction, or seizures • Prevention and management: leucovorin and can consider aminophylline or dextromethorphan
Emetic Risk	• Moderate emetic risk at doses $\geq$250 mg/m^2 ($5HT_3$ antagonist + corticosteroid +/- NK-1 receptor antagonist)
Mucositis	• Presents 5-10 days after MTX • Prevention and management: leucovorin, lifestyle modification, analgesics, antidiarrheals, and can consider palifermin

Ann Oncol 21 (Supp 5): v261–v265, 2010. | J Drug Metab Toxicol 2012;3:125. | Pediatr Neurol 2014; 50:625.

Antimetabolites: Pyrimidine Analogs

Cytarabine

Standard Dose Monitoring (100-200 mg/m^2/day IVCI)	High Dose Monitoring (1.5-3 g/m^2/dose)
• Myelosuppression **(DLT)** • Low emetic risk • Mucositis • Diarrhea • Alopecia	• Myelosuppression **(DLT)** • Moderate emetic risk: >200 mg/m^2 • Mucositis • Diarrhea • Alopecia • Neurotoxicity: cerebellar dysfunction – Typically reversible – Presents 3-8 days after 1st dose – Loss of balance, altered muscle tone, movement disorders, speech deficits, and/or nystagmus • Ocular toxicity: conjunctivitis – Prophylaxis with ophthalmic steroids – Dexamethasone 0.1% 1-2 drops in each eye Q6H starting 1 day prior and continued for 2-7 days after last dose • Dermatologic toxicity: hand-foot syndrome

Devita, Hellman, And Rosenberg's Cancer, 2009.

Antimetabolites: Pyrimidine Analogs

	Fluorouracil (5-FU) IV bolus or Continuous Infusion (IVCI)	**Capecitabine** Oral Fluorouracil Pro-drug

Monitoring Parameters	• Mucositis **(IVCI DLT)**
	• Diarrhea **(bolus > IVCI)**
	• Hand-foot syndrome **(IVCI only)**
	  - Palmar-plantar erythrodysesthesia
	  - Symptoms: redness, tenderness, peeling skin, numbness, blisters, and/or pain
	• Myelosuppression **(bolus > IVCI)**
	• Low emetic risk **(bolus > IVCI)**
	• Coronary vasospasm
	• Radiation sensitizer
	• Alopecia
	• Nail changes
	• Photosensitivity
		• Mucositis
		• Diarrhea
		• Hand-foot syndrome **(DLT)**
		  - Palmar-plantar erythrodysesthesia
		  - Symptoms: redness, tenderness, peeling skin, numbness, blisters, and/or pain
		• Minimal myelosuppression
		• Low emetic risk
		• Coronary vasospasm
		• Radiation sensitizer
		• Alopecia
		• Nail changes

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Devita, Hellman, And Rosenberg's Cancer, 2009. | Ther Adv Med Oncol. 2018 Jun 18;10.

Antimetabolites: Pyrimidine Analogs

Fluorouracil and Capecitabine

- Dihydropyrimidine dehydrogenase (DPD) deficiency
  - Metabolizes 5-FU to inactive metabolite
  - Deficiency results in severe toxicity
- Drug interactions
  - Leucovorin enhances 5-FU anticancer effects
  - Capecitabine and warfarin black box warning: clinically significant increase in INR
- Hand-foot syndrome prevention
  - Pyridoxine
  - Moisturize hand and feet
  - Avoid pressure, tight clothing, and hot water
  - Apply sunscreen
  - Wear gloves in winter or cold environments

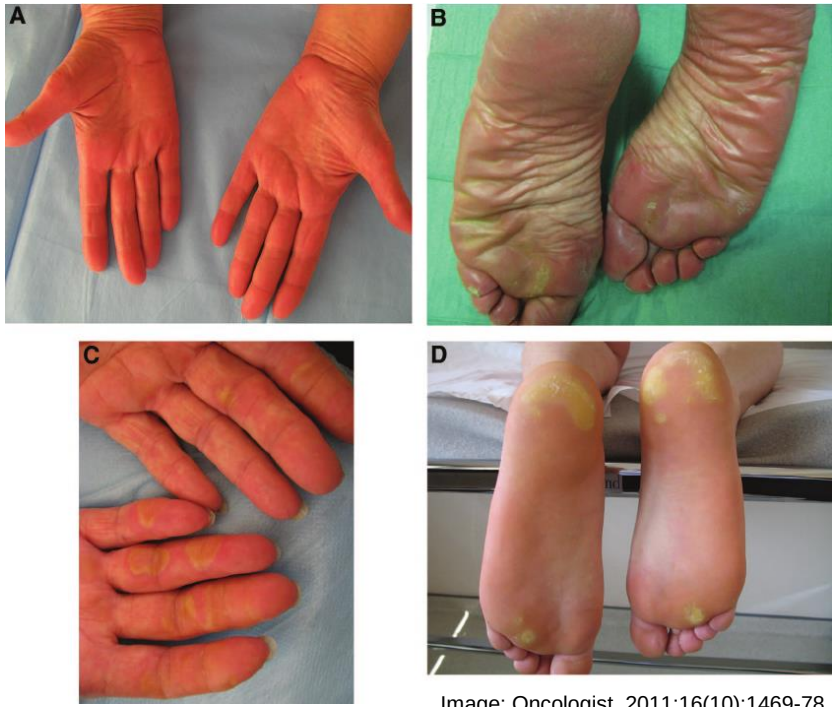

Image: Oncologist. 2011;16(10):1469-78.

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Antimicrotubular Agents: Taxanes

	Docetaxel	Paclitaxel

Monitoring Parameters	• Myelosuppression **(DLT)**
	  - Mostly neutropenia
	• Fluid retention (dose dependent)
	  - Dexamethasone 8 mg PO BID for 3 days, starting 1 day prior to docetaxel
	• Hypersensitivity reaction
	  - Due to polysorbate 80
	  - Dexamethasone premedication
	  - Slow infusion rate for mild reaction
	• Neuropathy (cumulative dose)
	• Mucositis
	• Alopecia
	• Low emetic risk
	• Cutaneous reaction
		• Myelosuppression **(DLT)**
		  - Mostly neutropenia
		  - Increased with longer infusion
		• Hypersensitivity reaction
		  - Due to cremophor solvent
		  - Steroid + H1RA + H2RA premedication
		• Peripheral neuropathy (cumulative dose)
		  - Increased with shorter infusion
		• Mucositis
		• Alopecia
		• Low emetic risk
		• Myalgia

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Devita, Hellman, And Rosenberg's Cancer, 2009.

Antimicrotubular Agents: Vinca Alkaloids

	Vincristine	Vinblastine	Vinorelbine
Common Indications	• Leukemia • Max dose = 2 mg	• Lymphomas and testicular cancer	• Lung cancer
Monitoring Parameters	• Neurotoxicity **(DLT)** • No myelosuppression • Constipation • Alopecia • Minimal emetic risk	• Least neurotoxic • Myelosuppression **(DLT)** • Constipation • Alopecia • Minimal emetic risk • Hypertension	• Less neurotoxicity • Myelosuppression **(DLT)** • Constipation • Alopecia • Minimal emetic risk
Clinical Considerations	• Implement bowel regimen pre and post vinca alkaloid dose • Extravasation management (vesicant) - Stop infusion immediately - Elevate affected extremity - Apply warm dry compresses for 20 minutes 4x/day for 1-2 days - Administer hyaluronidase 1 mL (150 units/mL) as 5 separate 0.2 mL injections subcutaneously into extravasation site • FATAL if given intrathecally - Dispense vinca alkaloids in a minibag of compatible solution and NOT in a syringe (ISMP)		

Devita, Hellman, And Rosenberg's Cancer, 2009. | Int J Prev Med. 2013 Nov;4(11):1231-5.

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  - Miscellaneous: bleomycin, mitomycin, mitoxantrone
- **Topoisomerase inhibitors**
  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    - Anthracyclines

Chemotherapy Drug Classes

- **Alkylating agents**
  - Alkyl sulfonates
  - Aziridines
  - Nitrogen mustards
  - Nitrosoureas
  - Platinum agents
  - Triazenes/Methylating agents
- **Antimetabolites**
  - DNA hypomethylating agents
  - Folate antagonists
  - Pyrimidine analogs
  - Purine analogs
  - Miscellaneous: hydroxyurea
- **Antimicrotubular agents**
  - Epothilones
  - Halichondrin B analogs
  - Taxanes
  - Vinca alkaloids
- **Antitumor antibiotics**
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- **Topoisomerase inhibitors**
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  - Topoisomerase II inhibitors
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Antitumor Antibiotics: Anthracyclines

	Doxorubicin	Daunorubicin	Idarubicin	Epirubicin
Drug Class Toxicities	• Myelosuppression**(DLT)** • Cardiotoxicity • More severe mucositis • Mod to high emetic risk • Alopecia • Red/orange urine • Radiation recall	• Myelosuppression**(DLT)** • Cardiotoxicity • Mucositis • Moderate emetic risk • Alopecia • Red/orange urine • Radiation recall	• Myelosuppression**(DLT)** • Less cardiotoxicity • Mucositis • Moderate emetic risk • Alopecia • Red/orange urine • Radiation recall	• Myelosuppression**(DLT)** • Less cardiotoxicity • Mucositis • Mod to high emetic risk • Alopecia • Red/orange urine • Radiation recall
Max Lifetime Dose	• 500 mg/m^2	• 550 mg/m^2	• 150 mg/m^2	• 900 mg/m^2
Clinical	• Extravasation management (vesicant) - Stop infusion immediately - Elevate affected extremity - Apply cold dry compresses for 20 minutes 4x/day for 1-2 days - Apply topical DMSO to a region covering twice the affected area every 8 hours for 7 days (do not cover with dressing) OR Dexrazoxane 1000 mg/m^2 on days 1-2, followed by 500 mg/m^2 on day 3			

Anthracycline Cardiotoxicity

- Mechanism
  - Cardiomyocyte damage via oxygen free radicals
- Risk factors
  - Cumulative dose
  - Age >65 years
  - Female gender
  - African Americans
  - Hypertension
  - Cardiac disease
  - Low baseline LVEF
  - Radiation or cardiotoxic drug exposure
- Cardiotoxic effects
  - Acute rhythm disruptions
  - Chronic heart failure
- Cardioprotective agents (EF 40-49%)
  - Dexrazoxane (Zinecard®)
    - Chelating agent interfering with iron mediated oxygen free radical generation
    - IV: 10:1 ratio of dexrazoxane:doxorubicin
  - Beta blockers: carvedilol or nebivolol
  - Angiotensin inhibition: enalapril or candesartan
  - Consider statin

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Devita, Hellman, And Rosenberg's Cancer, 2009. | Curr Cardiol Rev. 2011 Nov;7(4):214-20.

Antitumor Antibiotics: Bleomycin

- Pulmonary toxicity **(DLT)**
  - Oxygen free radical formation
  - Potentially life-threatening interstitial pulmonary fibrosis
- Administration
  - Anaphylactic reaction: consider test dose
  - Fever and chills: acetaminophen premedication
- Mucositis
- Alopecia
- Cutaneous reactions
  - Hyperpigmentation
  - Erythema
  - Skin peeling

Pulmonary Toxicity Risk Factors

- Cumulative dose >400 units (Max lifetime dose = 400 units)
- Age >40 years
- Smoking
- Chest irradiation
- Concurrent use of G-CSF

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Devita, Hellman, And Rosenberg's Cancer, 2009. | Ann Oncol. 2003 Jan;14(1):91-6.

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  - Topoisomerase II inhibitors
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Topoisomerase Inhibitor I: Irinotecan

- Myelosuppression **(DLT)**
  - Increased risk of neutropenia in patients with homozygous UGT1A1*28 allele
  - Decrease starting dose by at least one dose level
- Diarrhea **(DLT)**
  - Acute diarrhea (<24 hours): inhibition of acetylcholinesterase
    - Premedicate with atropine 0.25-1 mg IV or subcutaneously x 1
  - Delayed diarrhea (>24 hours): mucosal cytotoxicity
    - Loperamide 4 mg PO x 1 dose, then 2 mg every 2 hours until no diarrhea for 12 hours
    - Octreotide 100-150 mcg IV or subcutaneously every 8 hours
- Acute cholinergic effect
  - Symptoms include flushing, sweating, abdominal cramps, and/or diarrhea
  - Premedicate with atropine 0.25-1 mg IV or subcutaneously x 1
- Moderate emetic risk
- Alopecia

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Devita, Hellman, And Rosenberg's Cancer, 2009.

Question #1

- Which of the following chemotherapy agents is NOT correctly paired with its dose limiting toxicity?

A. Cisplatin: Nephrotoxicity

B. Vincristine: Neurotoxicity

C. Doxorubicin: Mucositis

D. Bleomycin: Pulmonary toxicity

E. Irinotecan: Diarrhea

Question #2

- Which of the following methods is NOT utilized for the primary prevention of HDMTX nephrotoxicity?

A. Aggressive fluid hydration
B. Urine alkalization via sodium bicarbonate
C. Leucovorin rescue
D. Glucarpidase therapy

Immunotherapy

Cancer Immunotherapy

- Type of therapy utilizing the immune system to elicit an anti-tumor response
- Passive immunotherapy: enhance existing immune system anti-tumor response
  - Immunomodulating antibodies
    - Immune co-stimulatory antibodies
    - Immune checkpoint inhibitors
  - Adoptive immunotherapy
    - Tumor infiltrating lymphocyte
    - Genetically modified T-cell receptors (TCRs)
    - Chimeric antigen receptors (CARs)
- Active immunotherapy: stimulate immune system response to attack cancer cells
  - Specific
    - Vaccines
    - Oncolytic viruses
  - Non-specific
    - Cytokines

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J Cancer. 2018 Apr 19;9(10):1773-1781.

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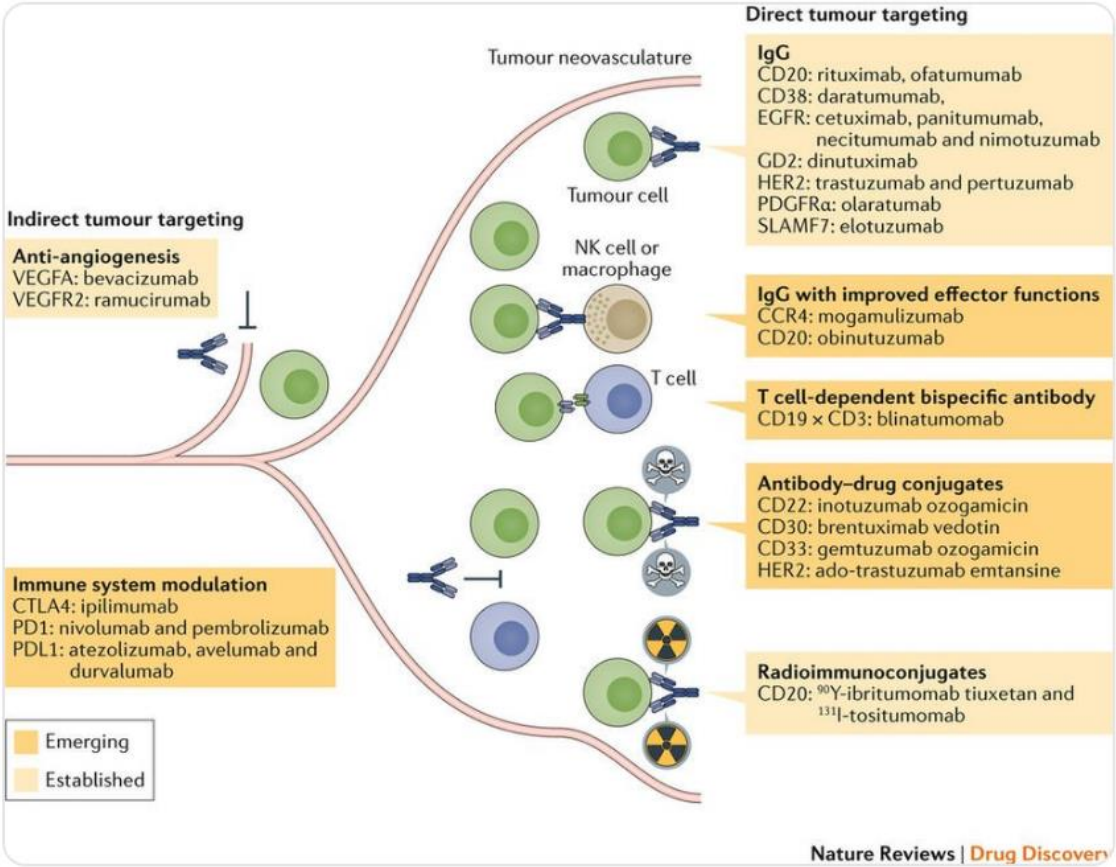
J Cancer. 2018 Apr 19;9(10):1773-1781.

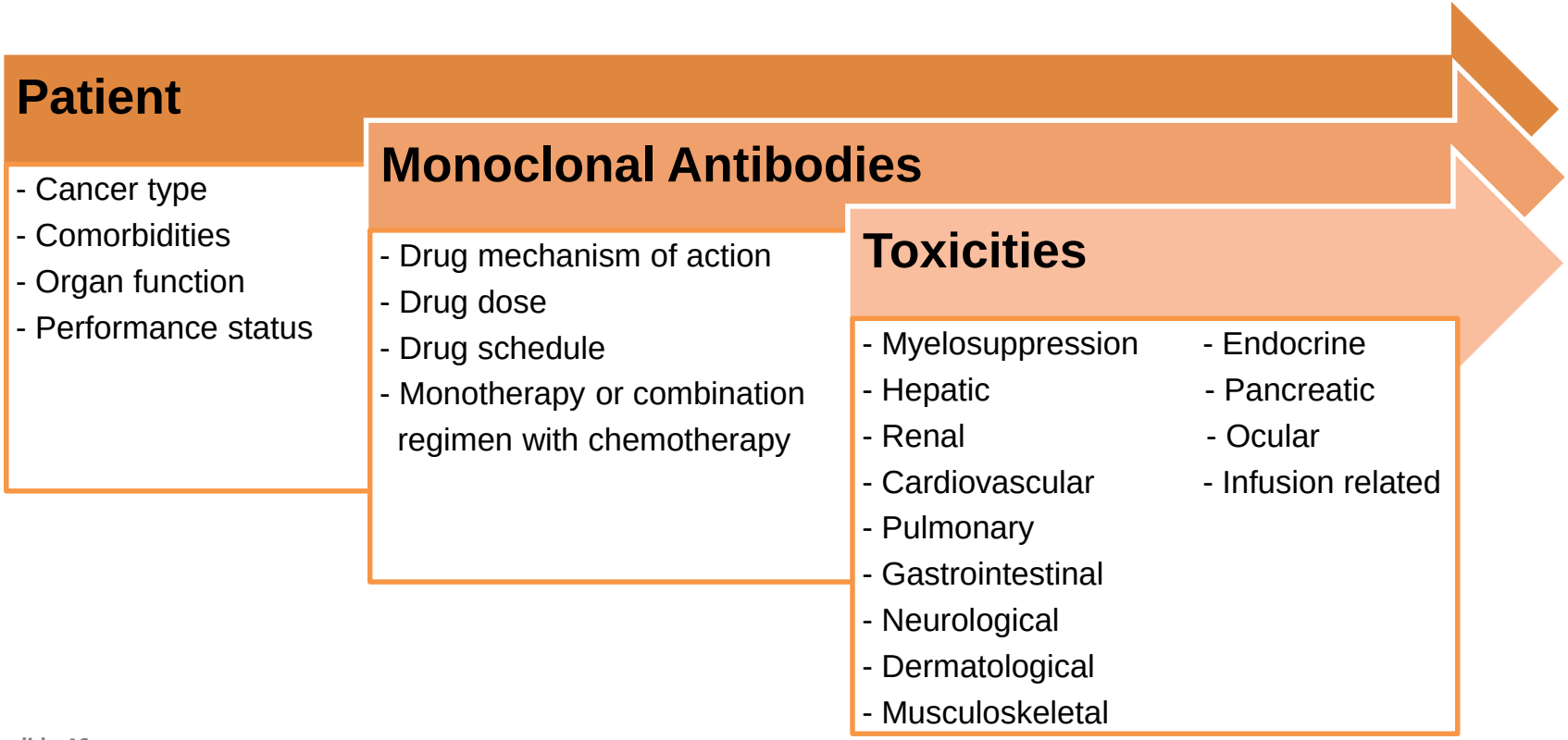
Antitumor Monoclonal Antibodies

- Antibody source
  - Murine/m**o**use (-**o**mab)
  - **Ch**imeric (-**xi**mab)
  - Humani**z**ed (-**zu**mab)
  - H**u**man (-**u**mab)
- Naked monoclonal antibodies
  - No modifications
  - Mechanism of action varies depending on molecular target
- Conjugated monoclonal antibodies
  - Combined with chemotherapy or radioactive agent
  - Deliver agent directly to cancer cell
- Bispecific monoclonal antibodies
  - Single agent comprised of two different monoclonal antibodies



Devita, Hellman, And Rosenberg's Cancer, 2009.
Nat Rev Drug Discov. 2018 Mar;17(3):197-223.

Immunotherapy Toxicity Overview



Lab Monitoring

CBC Monitoring for Immunotherapy

*Ado-trastuzumab (Kadcyla)**	Durvalumab (Imfinzi)*	Olaratumab (Lartruvo)*
Atezolizumab (Tecentriq)^	*Gemtuzumab (Mylotarg)**	Pembrolizumab (Keytruda)^
Bevacizumab (Avastin)*	Nivolumab (Opdivo)^	Ramucirumab (Cyramza)*
*Brentuximab (Adcetris)**	Obinutuzumab (Gazyva)*	Rituximab (Rituxan)
Daratumumab (Darzalex)*	Ofatumumab (Arzerra)	

*** = with each dose**
^ = every other dose
 # = weekly

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LFT Monitoring for Immunotherapy

*Ado-trastuzumab (Kadcyla)**	Elotuzumab (Empliciti)^	Obinutuzumab (Gazyva)*
Atezolizumab (Tecentriq)^	*Gemtuzumab (Mylotarg)**	Olaratumab (Lartruvo)*
*Brentuximab (Adcetris)**	Ipilimumab (Yervoy)*	Pembrolizumab (Keytruda)^
Durvalumab (Imfinzi)*	Nivolumab (Opdivo)^	

*** = with each dose**
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Lab Monitoring for Immunotherapy

Serum Creatinine
*Brentuximab (Adcetris)**
Durvalumab (Imfinzi)*
Nivolumab (Opdivo)^
Obinutuzumab (Gazyva)*
Pembrolizumab (Keytruda)^

Ejection Fraction (Baseline and every 3 months)
Ado-trastuzumab (Kadcyla)
Pertuzumab (Perjeta)
Trastuzumab (Herceptin)

Electrolytes (Mg/Ca/K at baseline, during treatment, and 8 weeks after treatment)
Cetuximab (Erbitux)

Thyroid Function Tests (Baseline and periodically)
Atezolizumab (Tecentriq)
Durvalumab (Imfinzi)
Ipilimumab (Yervoy)
Nivolumab (Opdivo)
Pembrolizumab (Keytruda)
Ramucirumab (Cyramza)

*** = with each dose**
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Lab Monitoring for Immunotherapy

- Hepatitis B virus (HBV) panel
  - Required prior to anti-CD20 monoclonal initiation
    - Box warning: risk for HBV reactivation resulting in fulminant hepatitis, hepatic failure, or death
    - Serology: hepatitis B surface antigen (HBsAg) and total hepatitis B core antibody (anti-HBc)
  - HBV reactivation occurs: discontinue anti-CD20 monoclonal
- Urine protein
  - Bevacizumab is associated with proteinuria and nephrotic syndrome
  - <2+ urine dipstick: continue to monitor
  - ≥2+ urine dipstick: further assessment via 24 hour urine collection
    - ≥2 g protein in 24 hours: stop bevacizumab and monitor
    - <2 g protein in 24 hours: restart bevacizumab
  - Nephrotic syndrome: discontinue bevacizumab

Hepatitis B Panel
Obinutuzumab (Gazyva)
Ofatumumab (Arzerra)
Rituximab (Rituxan)

Urine Protein
Bevacizumab (Avastin)*

*** = with each dose**
^ = every other dose
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Devita, Hellman, And Rosenberg's Cancer, 2009. | Oncologist. 2015 Feb;20(2):166-75.

Monoclonal Antibodies: Targeted Therapy

Immunotherapy: Targeted Therapy

Rituximab (Rituxan)	
Indications	• Lymphomas, leukemias, and autoimmune disorders
Target	• CD20 surface antigen on B-lymphocytes
Mechanism	• CD20 antigen binding results in complement dependent B-cell cytotoxicity and lysis
Monitoring Parameters	

HBV reactivation	• HBV screening prior to initiation - HBsAg and Anti-HBc
Hypersensitivity reactions	• Hypotension, angioedema, bronchospasm, and/or urticaria • 80% of fatal reactions occurred with first infusion
Infusion related reactions	• Chills, fever, rigors, dizziness, rash, and/or nausea/vomiting • Pretreatment: acetaminophen + diphenhydramine +/- steroids
Mucocutaneous reactions	• Stevens-Johnson syndrome, toxic epidermal necrolysis, and others
Lymphopenia	• Avoid live vaccines during treatment

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Devita, Hellman, And Rosenberg's Cancer, 2009. | Rituximab [package insert] 2019.

Immunotherapy: Targeted Therapy

Bevacizumab (Avastin)		
Indications	• Colorectal, cervical, ovarian, renal, lung cancer, and glioblastoma	
Target	• Vascular endothelial growth factor (VEGF)	
Mechanism	• Binds to VEGF and inhibits angiogenesis • Reduces proliferation of endothelial cells	
Monitoring Parameters	Severe or fatal hemorrhage	• Bleeding episodes 5x greater in bevacizumab patients • Hemoptysis, epistaxis, GI bleed, CNS bleed, or vaginal bleed • Avoid in patients with recent history of hemoptysis
	GI perforation	• Incidence: 0.3 - 3%
	Wound healing impairment	• Withhold bevacizumab for at least 28 days prior to surgery • Do not administer for at least 28 days after surgery and until wound has healed
	Hypertension	• May cause or worsen hypertension • Treat with anithypertensives (consider ACE-i or ARB if proteinuria)
	Thrombosis	• Caution before initiating if patient has new thrombosis
	Proteinuria	• Monitor prior to each dose

Devita, Hellman, And Rosenberg's Cancer, 2009. | Bevacizumab [package insert] 2018.

Immunotherapy: Targeted Therapy

Trastuzumab (Herceptin)	
Indications	• Breast and gastric cancer
Target	• Human epidermal growth factor receptor 2 (HER-2)
Mechanism	• Binds to HER-2 inducing cytotoxicity of cells overexpressing HER-2 protein
Monitoring Parameters	

Cardiomyopathy **(DLT)**	• Type II: reversible damage and not related to cumulative dose • Evaluate LVEF prior to and during treatment • Highest risk in patient receiving concomitant anthracycline
Infusion reactions	• Serious and fatal reactions can occur • Fever, chills, rash, dizziness, pain, nausea, dyspnea, and/or hypotension • Symptoms occur during or within 24 hours of administration
Pulmonary toxicity	• Dyspnea, hypoxia, interstitial pneumonitis, pleural effusion, edema, and/or pulmonary fibrosis • Use with caution in pre-existing pulmonary disease or tumor

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Devita, Hellman, And Rosenberg's Cancer, 2009. | Trastuzumab [package insert] 2018.

Question #3

- Which of the following immunotherapy agents is NOT correctly paired with its key lab monitoring parameter?

A. Brentuximab: Complete blood count

B. Trastuzumab: Ejection fraction

C. Cetuximab: Thyroid function tests

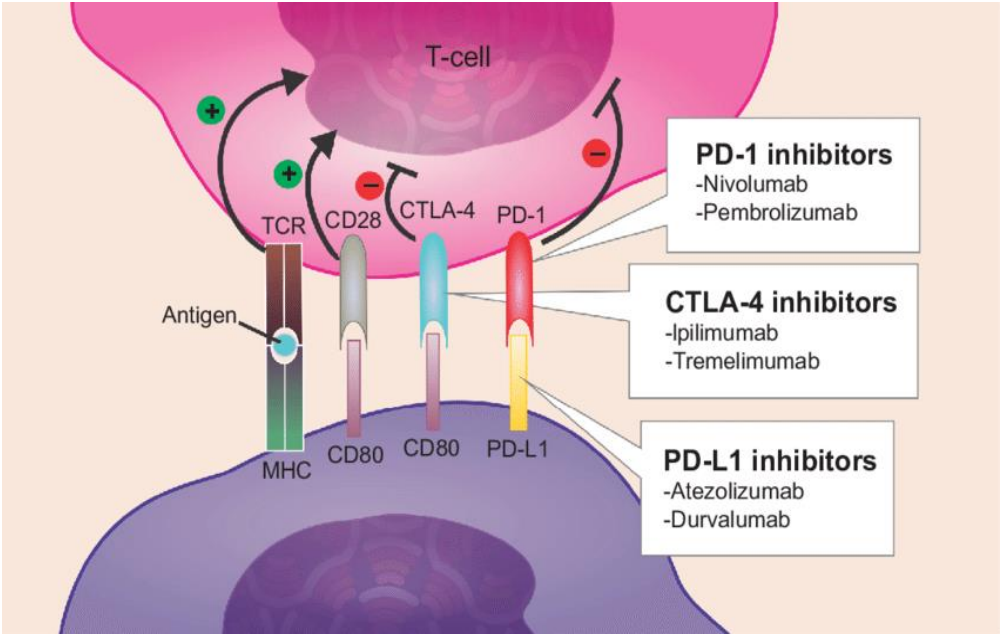
D. Rituximab: Hepatitis B panel

E. Bevacizumab: Urine protein

Monoclonal Antibodies: Checkpoint Inhibitors

Immune Checkpoint Inhibitors

- Mechanism of action
  - Immune system homeostasis
    - Checkpoint proteins used to differentiate between normal and foreign cells
    - Immune response requires activation or inactivation of checkpoint proteins
  - Cancer cells evade immune antitumor response by utilizing checkpoint proteins
  - Checkpoint inhibitors enhance immune antitumor recognition and response
- T-cell checkpoint targets
  - Programmed cell death-1 (PD-1)
  - PD-1 ligand (PD-L1)
  - Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)



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Onco Targets Ther. 2016 Dec 16;10:21-30.

Immunotherapy: Checkpoint Inhibitors

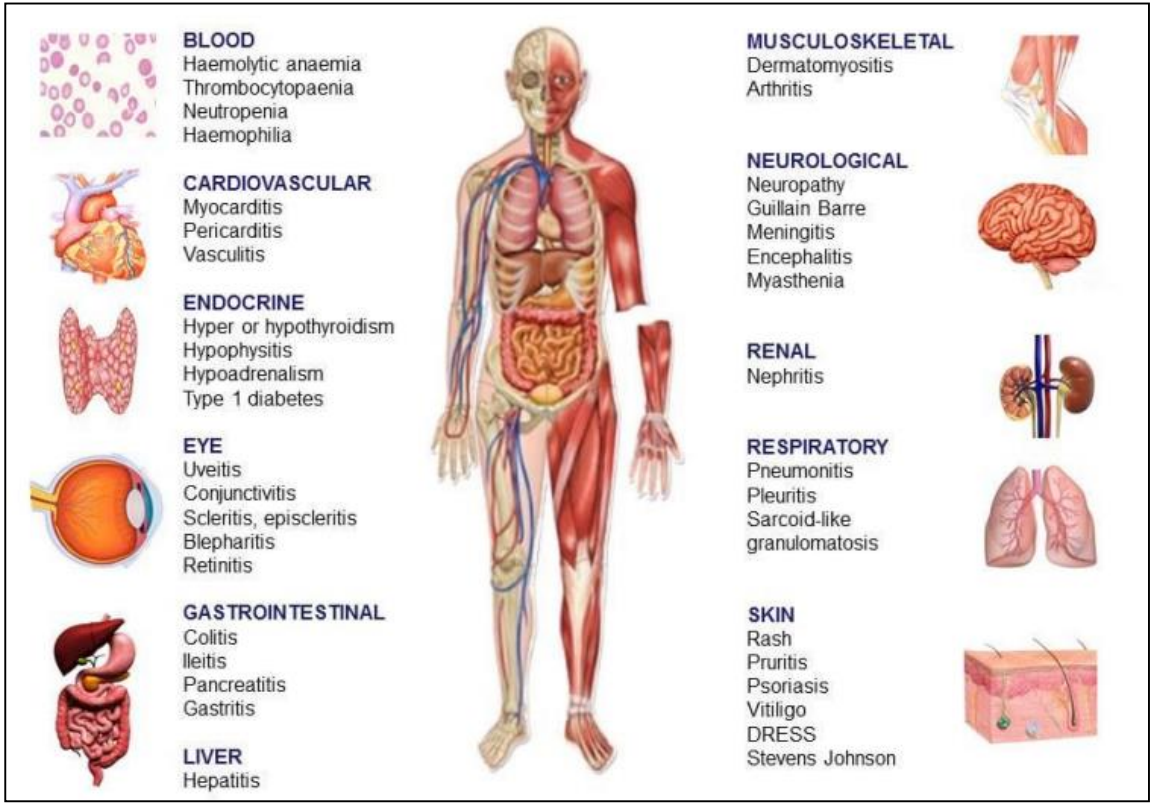
Ipilimumab (Yervoy)	
Indications	• Melanoma
Target	• Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)
Mechanism	• Binds and inhibits CTLA-4, resulting in enhanced T-cell activation and proliferation • Combination therapy with nivolumab provides synergistically superior T-cell enhancement

Nivolumab (Opdivo) and Pembrolizumab (Keytruda)	
Nivolumab Indications	• Colorectal, head and neck, hepatic, renal, urothelial, lung cancer, melanoma, and Hodgkin lymphoma
Pembrolizumab Indications	• Gastric, head and neck, urothelial, lung cancer, melanoma, and Hodgkin lymphoma
Target	• Programmed cell death 1 (PD-1)
Mechanism	• Binds to PD-1 receptor, which prevents PD-L1 from binding • Results in T-cell activation and proliferation

Onco Targets Ther. 2016 Dec 16;10:21-30.

Immune Checkpoint Inhibitor Toxicity

- Toxicity
  - Relatively delayed onset
  - Inflammation
  - Autoimmune nature
- Pathophysiology
  - Unknown mechanism
  - Potentially due to T-cell activity on tumor and healthy cells



NCCN: Management of Immunotherapy-Related Toxicities Guidelines, 2019. | Immunotherapy. 2018 Apr; 42(1): 11-12

Immune Checkpoint Inhibitor Toxicity

- Incidence of immune related adverse events (irAE)
  - CTLA-4 inhibitors
    - Any grade irAE: 72%
    - High grade irAE: 24%
    - Fatal irAE: 1.08%
    - irAE seem dose dependent
  - PD-1/PD-L1 inhibitors
    - Any grade irAE: 30%
    - High grade irAE: 6%
    - Fatal irAE: 0.37%
    - irAE less dose dependent and vary by disease site

CLTA-4, PD-1, and PD-l1 Common Toxicities

- Infusion reactions
- Chills
- Fever
- Diarrhea
- Colitis
- Rash
- Pruritus
- Fatigue
- Hepatitis
- Endocrine

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NCCN: Management of Immunotherapy-Related Toxicities Guidelines, 2019.

Checkpoint Inhibitor Toxicity Management

CTCAE Criteria	irAE Severity	General Management Strategy
Grade 1	• Asymptomatic • Mild symptoms	• **Observation** • **No intervention required**
Grade 2	• Moderate symptoms	• **Consider holding therapy and provide local or noninvasive intervention** - Resume therapy when symptoms and/or labs decrease below grade 1 - If symptoms >1 week: initiate prednisone 0.5 - 1 mg/kg/day - If symptoms >6 weeks: permanently discontinue therapy
Grade 3	• Several symptoms • Medically significant	• **Stop immunotherapy, consider hospitalization, and start high dose steroids** - Prednisone 1 - 2 mg/kg/day or equivalent (taper when grade 1) - If patient receives prednisone ≥20 mg/day x 4 weeks: PCP prophylaxis - Consider alternative immunosuppressive agents if symptoms >3 days on IV steroids: infliximab 5 mg/kg, mycophenolate mofetil, or other agents
Grade 4	• Life threatening	• **Permanently stop immunotherapy, require hospitalization, high dose steroids** - Prednisone 2 mg/kg/day or equivalent (taper when grade 1) - If patient receives prednisone ≥20 mg/day x 4 weeks: PCP prophylaxis - Consider alternative immunosuppressive agents based on toxicity if needed: infliximab, mycophenolate, cyclophosphamide, cyclosporine, IVIG, or others
Grade 5	• Death due to AE	

Front Pharmacol. 2017 Feb 8;8:49. | NCCN: Management of Immunotherapy-Related Toxicities Guidelines, 2019.

Questions?

Monitoring Parameters for Chemotherapy and Immunotherapy

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References

- Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity. Pediatr Neurol 2014; 50:625.
- Ahmed YAA, Hasan Y. Prevention and Management of High Dose Methotrexate Toxicity. J Cancer Sci Ther. 2013;5: 106-112.
- Avan A, Postma TJ, Ceresa C, et al. Platinum-induced neurotoxicity and preventive strategies: past, present, and future. Oncologist. 2015 Apr;20(4):411-32.
- Avastin (bevacizumab) [package insert]. San Francisco, CA: Genentech Inc; June 2018.
- Brandes AA, Bartolotti M, Tosoni A, Poggi R, Franceschi E. Practical management of bevacizumab-related toxicities in glioblastoma. Oncologist. 2015 Feb;20(2):166-75.
- Brown MP, Mislang A. Cancer immunotherapy: at a new immune frontier. Immunotherapy. 2018 Apr; 42(1): 11-12
- Carter PJ, Lazar GA. Next generation antibody drugs: pursuit of the 'high-hanging fruit'. Nat Rev Drug Discov. 2018 Mar;17(3):197-223.
- De Mello RA, Veloso AF, Esrom Catarina P, Nadine S, Antoniou G. Potential role of immunotherapy in advanced non-small-cell lung cancer. Onco Targets Ther. 2016 Dec 16;10:21-30.
- DeVita V, Lawrence T, Rosenberg S. Devita, Hellman, And Rosenberg's Cancer: Principles & Practice of Oncology. 9th Ed. Lippincott Williams & Wilkins; 2009.
- Drilon A, Postow M, Krug L et al. Pocket Oncology. 1st ed. Wolters Kluwer Health; 2014:58-88.
- Florescu M, Cinteza M, Vinereanu D. Chemotherapy-induced Cardiotoxicity. Maedica (Buchar). 2013 Mar;8(1):59-67.
- Gaies E, Jebabli N, Trabelsi S, et al. Methotrexate Side Effects: Review Article. J Drug Metab Toxicol. 2012;3:125.

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References

- Herceptin (trastuzumab) [package insert]. San Francisco, CA: Genentech Inc; November 2018.
- Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist. 2016;21:1-12.
- Kumar V, Chaudhary N, Garg M, et al. Current Diagnosis and Management of Immune Related Adverse Events (irAEs) Induced by Immune Checkpoint Inhibitor Therapy. Front Pharmacol. 2017 Feb 8;8:49.
- LaCasce, AS. Therapeutic use and toxicity of high-dose methotrexate. In: UpToDate, Maki R, Freedman AS, Pappo AS (Eds), UpToDate, Waltham, MA. Accessed on December 21, 2018.
- Meadors M, Floyd J, Perry MC. Pulmonary toxicity of chemotherapy. Semin Oncol. 2006 Feb;33(1):98-105.
- Mehmood RK. Review of Cisplatin and oxaliplatin in current immunogenic and monoclonal antibody treatments. Oncol Rev. 2014 Sep 23;8(2):256.
- Moudi M, Go R, Yien CY, Nazre M. Vinca alkaloids. Int J Prev Med. 2013 Nov;4(11):1231-5.
- National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2019: Management of Immunotherapy-Related Toxicities, 2019.
- O'Sullivan JM, Huddart RA, Norman AR, Nicholls J, Dearnaley DP, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol. 2003 Jan;14(1):91-6.
- Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guiidelines. Ann Oncol 21 (Supp 5): v261–v265, 2010.
- Rituxan (rituximab) [package insert]. San Francisco, CA: Genentech Inc; January 2019.

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References

- Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol. 2018 Jun 18;10.
- Schwartz S, Borner K, Müller K, et al. Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. Oncologist. 2007 Nov;12(11):1299-308.
- Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011 Nov;7(4):214-20.
- Zhang H, Chen J. Current status and future directions of cancer immunotherapy. J Cancer. 2018 Apr 19;9(10):1773-1781.

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