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Oncologic Pharmacology for the Rehabilitation Professional

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- Presenter Disclosure: Financial: Stephen Morris has received an honorarium for presenting this course. Non-financial: Stephen Morris has no relevant non-financial relationships to disclose.

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CONTINUED

Learning Outcomes

After this course, participants will be able to:

- Identify at least three strategies for administration of chemotherapeutic agents using fundamental principles of pharmacology.
- Define the fundamental mechanisms of action of at least three of five different classes of chemotherapeutic agents.
- Identify at least three management strategies for the adverse effects of specific chemotherapeutic agents.

INTRODUCTION

Definitions

- Pharmacology: The study of drugs
  - Pharmacokinetics
    - The study of how the body deals with a drug in term of absorption, distribution and elimination
  - Pharmacodynamics
    - The study of what a drug does to the body including its mechanism of action
  - Toxicology*
    - The study of the harmful effects of a drug

Definitions

- Oncology:
  - A branch of medicine that specializes in the diagnosis and treatment of cancer
    - NCI
  - A branch of medicine concerned with the prevention, diagnosis, treatment, and study of cancer
    - Merriam Webster Dictionary

Definitions

- Chemotherapy
  - The treatment of disease by the use of chemical substances
  - By definition this includes antibiotics, antifungals, anti-inflammatory drugs, etc.
  - But today, “chemo” has become almost exclusively linked to drugs used in the treatment of cancer

Chemotherapy- An Interesting Beginning

- 2nd half of the 19th century
  - 1860- Sulfur mustard was first synthesized by F. Gutherie
  - Named because it smelled of “oil of mustard”
  - Caused severe skin blistering, had a long latency period and the wounds were slow to heal

Chemotherapy- An Interesting Beginning

- WW1-1914-198
  - Sulphur mustard was widely used as a chemical warfare agent by both sides
  - Effects range from minor skin irritation to severe lung damage when inhaled
  - Pancytopenia

Chemotherapy- An Interesting Beginning

- WWII
  - Studied and used as a biological warfare agent.
  - 1942: Goodman & Gilman showed it could reduce tumor size [lymphosarcomas] in mice
  - Human Drug trial [N=1]
  - Bari Harbor and USS Harvey (1943)
  - Release of mustard gas during German air raid
  - Stewart F Alexander, MD confirmed pancytopenia in civilian and military causalities

Chemotherapy- An Interesting Beginning

- Post WWII
  - 1946: 3 Clinical trials involving patients with Hodgkin's Disease, Non-Hodgkin's Lymphoma and leukemia were conducted and showed clinical benefit
  - The molecule was declassified & approved for civilian use launching the era of modern chemotherapy

What is the Linkage Between Sulfur Mustard gas and Cancer?

- Sulfur mustard
  - Alkylating agent
  - **Cytotoxic**: Toxic to living cells
  - Causes cross-links to be formed between strands of the DNA double helix or within a single DNA strand
  - Prevents the double stranded DNA from untwisting or unzipping thus preventing DNA replication and hence cell replication

What is the Linkage Between Sulfur Mustard Gas and Cancer?

- Blood cells are rapidly reproducing cells
  - RBCs: 2 million RBCs manufactured per second
  - 2,400,000,000 RBCs manufactured during this talk
- Blood cells production is known to be curtailed by sulfur mustard resulting in pancytopenia

What is the linkage between Sulfur Mustard Gas and Cancer?

- Cancer- Diseases in which cells undergo uncontrolled growth resulting in abnormal cells which can invade nearby tissues.
- With cancer:
  - Cells grow when they should not; the accelerator is always turned-on, and brakes are turned off
  - Those signals that tell a defective cell to die remain turned off
  - Those signals that instruct a cell to survive are always turned-on

"The rest of the story"

- Blood cells and tumor cells are both rapidly reproducing cells
- By extension, suppression of cell growth by sulphur mustard could be of benefit to manage a cancer
- Clinical trials began in 1946
- Set into motion the development of new use of chemotherapeutic agents
- All interfered with cell replication in some fashion

PHARMACOLOGY BASICS

Adverse Effects of Cancer Treatment

- "Adverse drug reaction (ADR) is a broad term referring to unwanted, uncomfortable, or dangerous effects that a drug may have."
  - Merk Manual
- "An adverse drug reaction is an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product" Coleman JJ. Clinical Medicine. 2016

Acute adverse Effects of Cancer Treatment

- Pancytopenia
- Anemia
- Hair Loss (Alopecia)
- N&V and other GI tract side effects
- Peripheral Neuropathy
- Easy bruising (thrombocytopenia)
- Infection
- Chemo brain/brain fog

Long Term Adverse Effects of Cancer Treatment

- These are side effects that arise during treatment and may persist after treatment has concluded
  - Fatigue
  - Chemobrain/chemofog
  - Lymphedema
  - Peripheral Neuropathy
  - Functional deficits
  - Pulmonary dysfunction

Late (Latent) Effects of Cancer Treatment

- Adverse effects that emerge months to years after cancer treatment has been completed
  - Lymphedema
  - Heart failure
  - Pulmonary dysfunction
  - Increased risk for developing cardiovascular risk factors
  - Premature menopause

FDA & Nutritional Supplements

- A dietary supplement:
  - Is intended for ingestion
  - Contains an ingredient(s) intended to add further nutritional value to the diet
  - Includes: Vitamins, minerals, herbs, amino acids, concentrate, metabolite, constituent or extract

FDA & Nutritional Supplements

- The dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed
- FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market
- Manufacturers must make sure that product label information is truthful and not misleading

What are the Goals of Systemic Chemotherapy?

- Cure
- Increased survival/lengthened survival
- Palliate symptoms through disease control

Neoadjuvant Therapies

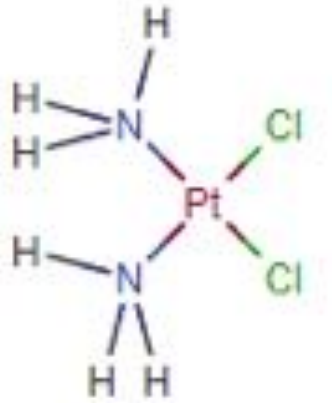
- Neoadjuvant therapies are therapies delivered before the main treatment to reduce tumor size or kill cancer cells that have spread
  - Preoperative chemotherapy
  - Preoperative radiation
  - Anthracycline based (doxorubicin) or Taxane based chemotherapies for breast cancers
  - Cisplatin, methotrexate & ifosamide-osteosarcomas
  - Q3

Adjuvant Chemotherapy

- Adjuvant/preventive treatment – provided when there is a high risk of recurrence with local treatment alone
  - Delivered after the primary treatment
  - 5-FU after surgery for colorectal cancer
  - Herceptin after breast cancer surgery
  - Cisplatin after lung resection for NSCLC
  - Goal is to increase overall survival
  - Balanced against risk of experiencing adverse effects

Drug Nomenclature

- **Chemical Name:** cis-diamminedichloroplatinum(II) (CDDP)
- **Generic Name:** cisplatin
- **Trade/Proprietary name:** Platinol



- Trade/proprietary names are usually capitalized
- Generic names are not

Drug Nomenclature: Examples

Generic Names	Proprietary name or brand name)
busulfan	Myleran
carmustine	BCNU
cyclophosphamide	Cytoxan, Neosar Cyclophosphamide
dacarbazine	DTIC-Dome
lomustine	Ceenu, Gleostine
mechlorethamine	Mustargen Nitrogen Mustard

Chemotherapeutic Agents

- "Many chemotherapeutic agents are systemic and nonspecific, which means they can reach and exert their toxic effects on noncancerous cells as well"
- Goodman & Gillman
- Personalized cancer medicine [targeted therapy]
  - Chemotherapy treatments are predicated on the tumor's genes and/or specific biochemical defects
  - Target specific biochemical pathways that regulate cell growth in some fashion

Tumor Growth Fraction

- The tumor growth fraction of a solid tumor refers to the percentage of cells engaged in the proliferation phase of the growth cycle at any given point in time.

- Tumor burden refers to the number of cancer cells present in the tumor

Fractional Kill or Fractional Cell Kill

- Fractional Kill
  - The fractional kill hypothesis states that a defined chemotherapy concentration, applied for a defined time period, will kill a constant fraction of the cells in a population, independent of the absolute number of cells

Concept of Total Cell Kill

- Because each dose kills only a fraction of the cancer cells, repeated doses of a chemotherapeutic drug must be delivered to eliminate the tumor
- Complete elimination of cancer cells require multiple dosing:
  - Assuming a tumor burden of 1011 cells and a 99% kill rate per cycle, 6 cycles are required to reduce the tumor burden to < 1 cell

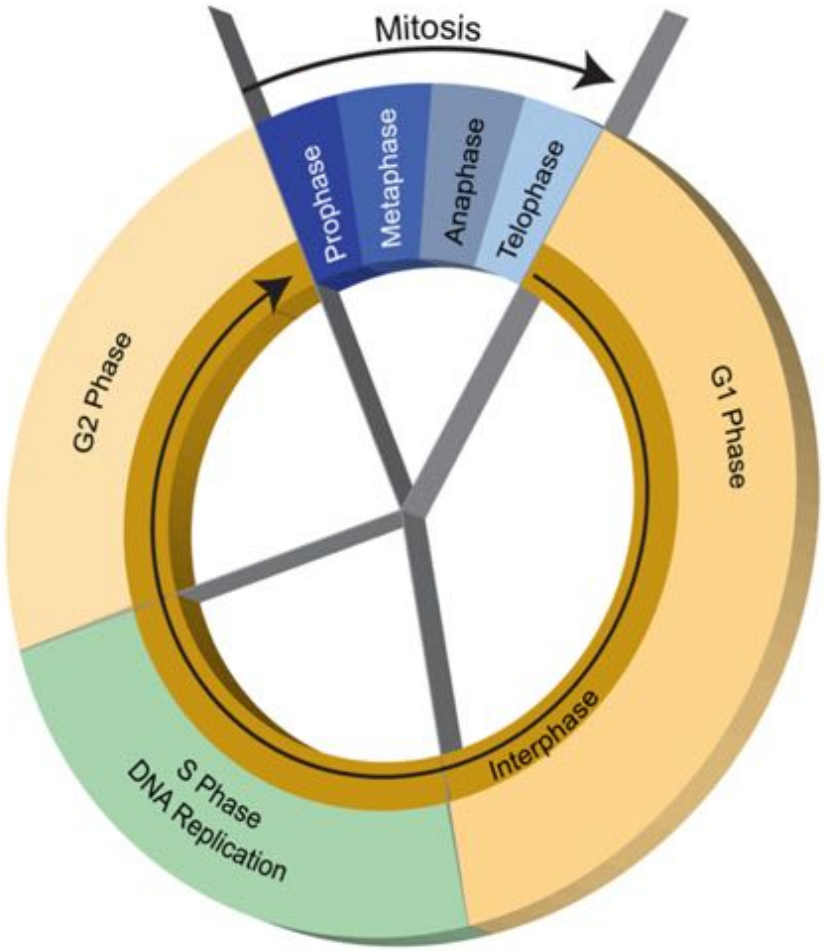
Concept of Total Cell Kill

Round #	Number of Cancer Cells Present			Number of cells remaining
1	1×10^{11}	X	1×10^{-2}	1×10^{9}
2	1×10^{9}	X	1×10^{-2}	1×10^{7}
3	1×10^{7}	X	1×10^{-2}	1×10^{5}
4	1×10^{5}	X	1×10^{-2}	1×10^{3}
5	1×10^{3}	X	1×10^{-2}	1×10^{1}
6	1×10^{1}	X	1×10^{-2}	1×10^{0}

Concept of Total Cell Kill

- Combined Chemotherapy Regimens
  - FAC: 5-fluorouracil, doxorubicin (Adriamycin), cyclophosphamide (Cytoxan): used to treat breast cancer
  - CHOP: Cytoxan (cyclophophomide), doxorubicin (Adriamycin), Oncovin (vincristine), prednisone. Used to treat Non-Hodgkin's lymphoma

Cell Cycle



Credit: National Institutes of Health

Combined Chemotherapy Regimens

- Each drug is active against a particular tumor or tumors
- Drugs typically differ in their site of action
- Drugs typically differ in their time of effectiveness in terms of the cell cycle
- Drugs have different toxicity levels
- Nadirs occur at different times
  - Nadir: low point of a sign (blood count) or symptom
  - The nadir time is usually about 10 days after treatment

Prednisone and other corticosteroids

- Cortisone, hydrocortisone and prednisone
- Immunosuppressive and anti-inflammatory drugs
  - Limit edema (Brain tumors)
  - Limit immune function itself (GVHD)
- Adverse Effects
  - Fluid retention
  - High blood pressure
  - Hyperglycemia
  - Osteoporosis
  - Proximal muscle weakness of the limbs

How are chemotherapeutic agents delivered?

- Orally
- Sub-Q injections
- Topical
- IM injections
- IV administration
- PICC
- “Ports”
- Intraventricular/Intrathecal

Factors Considered in Developing a Chemotherapy Regime

- Tumor Factors
  - Stage
  - Pathological features/genetics
  - Treatment intent

- Patient Factors
  - Fitness for treatment
  - Co-Morbidities
  - Patient Wishes

Chemotherapy Drugs: Classification and Mechanisms of Action

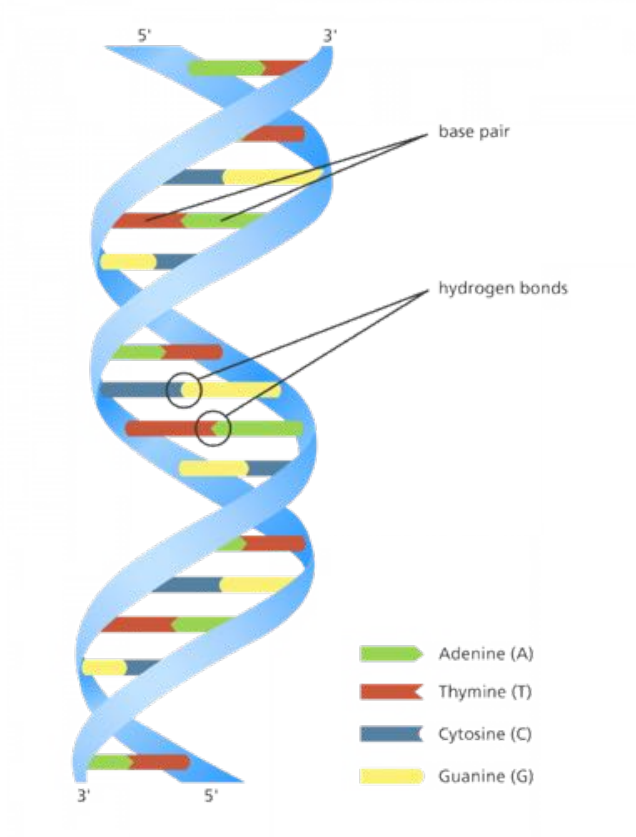
Types of Drugs used in Cancer Treatment

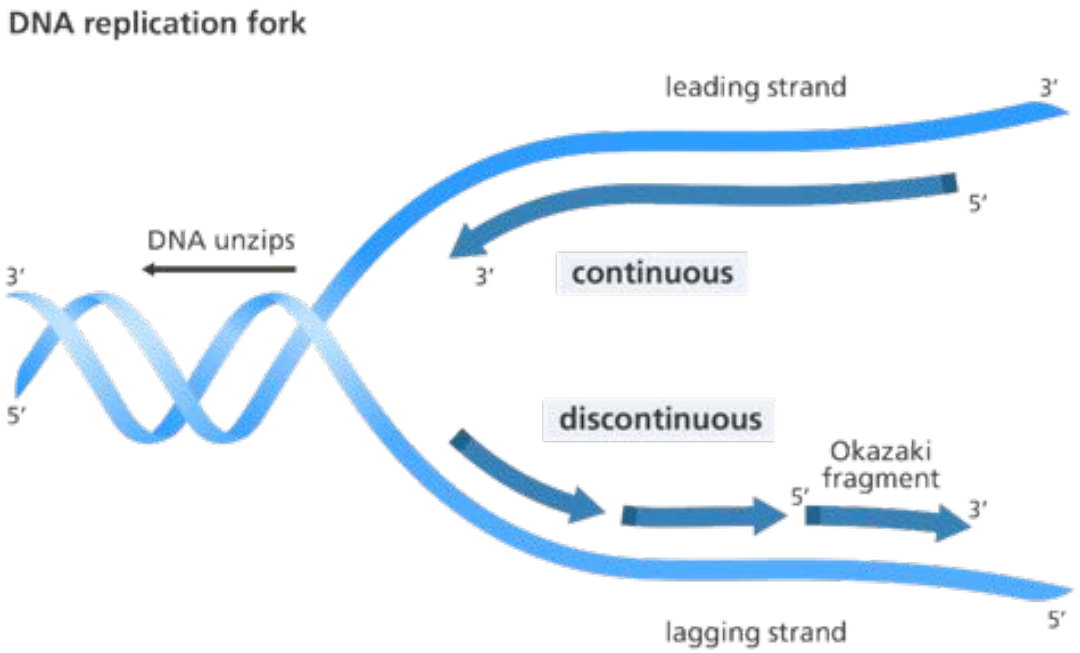
- Conventional/cytotoxic [Legacy]
- Immune Checkpoint Inhibitors
- Monoclonal Antibodies
- Vaccines
- Immune System Modulating Drugs
- T-cell transfer therapy
- Hormone Therapy
- Targeted Therapy

Cytotoxic drugs

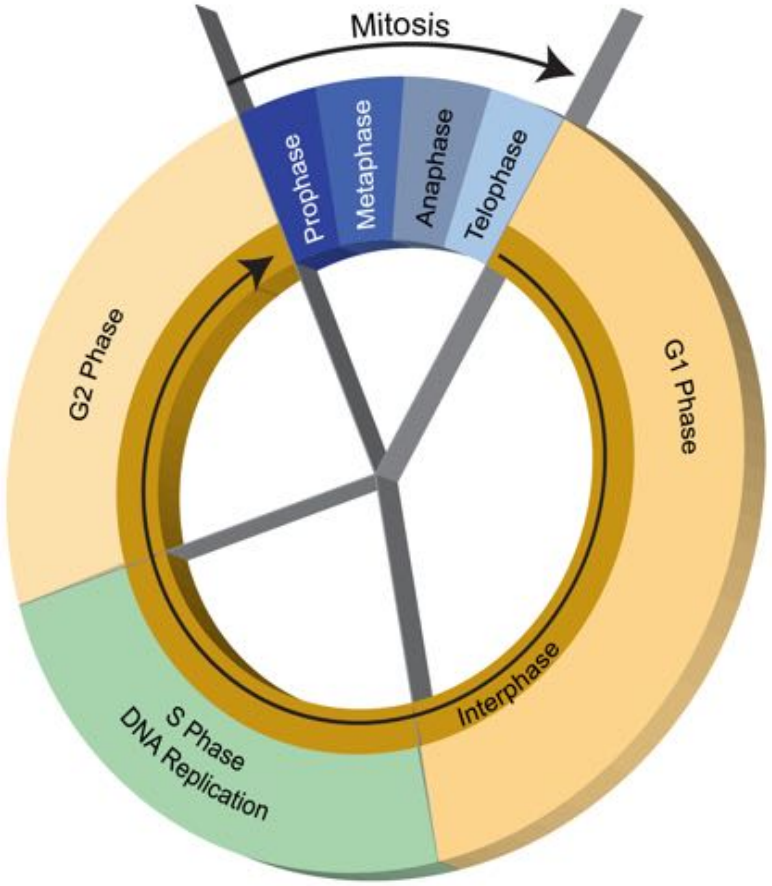
Chemotherapeutic Drugs (Cytotoxic)

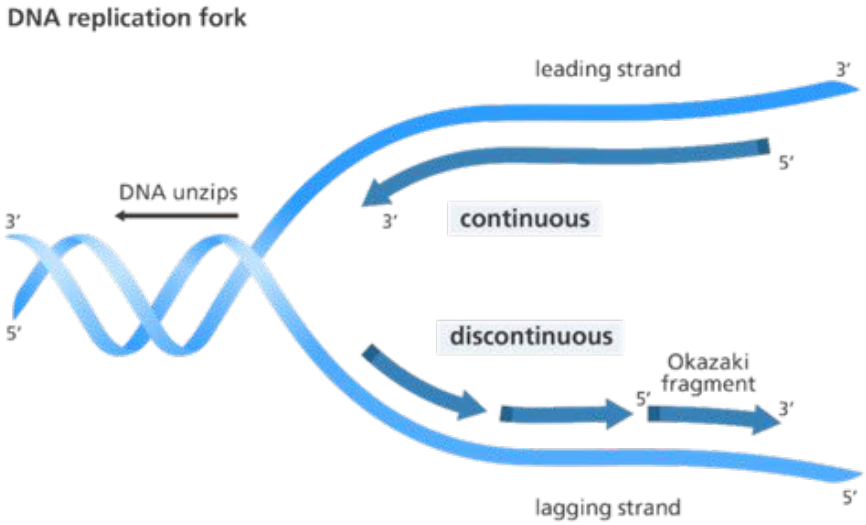
- These drugs have been around a long time
- Over 50 different cytotoxic drugs available
- These drugs are systemic in there actions
- These drugs take advantage of the fact that cancer cells are rapidly dividing (high mitotic rate)
- These drugs can not distinguish healthy cells from cancer cells





yourgenome, Genome Research Limited. https://www.yourgenome.org/facts/what-is-dna-replication





yourgenome, Genome Research Limited. https://www.yourgenome.org/facts/what-is-dna-replication

Credit: National Institutes of Health

Cytotoxic Drugs

- Cytotoxic: toxic to cells
- Delivered systemically
- Healthy cells with high mitotic rates are adversely affected by cytotoxic drugs (epithelial cells)
  - Cells that make up epithelial layers-GI tract
  - Bone marrow cells
  - Hair cells
- But nearly every organ in the body can be adversely affected by these cytotoxic drugs

Categories of Cytotoxic Drugs

ALKYLATING AGENTS	ANTI-METABOLITES	MITOTIC INHIBITORS	ANTIBIOTICS	OTHERS
BUSULFAN	CYTOSINE	ETOPOSIDE	BLEOMYCIN	L-ASPARAGINASE
CARMUSTINE	ARABINOSIDE	TAXOIDS	DACTINOMYCIN	HYDROXYUREA
CHLORAMBUCIL	FLOXURIDINE	VINBLASTINE	DAUNORUBICIN	PROCARBAZINE
CISPLATIN	FLUOROURACIL	VINCRISTINE	DOXORUBICIN	
CYCLOPHOSPHAMIDE	MERCAPTOPURINE	VINDESINE	MITOMYCIN-C	
IFOSFAMIDE	METHOTREXATE		MITOXANTRONE	
MELPHALAN			PLICAMYCIN	

Cytotoxic Chemotherapeutic Agents: Alkylating Agents

- Disrupt the integrity of the DNA strands
  - Insert themselves into the DNA strand, breaking or disrupting the strand
  - Cause DNA crosslinking
- These structural defects in the DNA prevent successful and/or correct DNA replication
- Cell replication is compromised.

Cytotoxic Chemotherapeutic Agents: Alkylating Agents

- Examples:
  - Busulfan (Myleran) — Myelosuppression
  - Cisplatin (Platinol) — Neurotoxicity (peripheral neuropathy)
  - Carboplatin
  - Oxaliplatin
  - Cyclophosphamide (Cytoxan) — Hemorrhagic cystitis
  - Ifosfamide
- Used to treat many solid and hematological tumors

Cytotoxic Chemotherapeutic Agents: Antimetabolites

- These drugs are structurally similar to the purine and pyrimidine bases that form the bridges between each DNA strand.
- Act by:
  - Being incorporated into the DNA strand, leading to the synthesis of a defective DNA strand
  - Inhibiting enzymes necessary for DNA and RNA replication, as well as protein synthesis

Antimetabolites

- Examples
  - 5-fluorouracil (5-FU)
  - Cytarabine (Ara-C)
  - Methotrexate
  - Gemcitabine
  - Pentostatin
- Used to treat colorectal, breast and pancreatic cancers

Cytotoxic Chemotherapeutic Agents: Antibiotics

- These drugs are not like the antibiotics used to treat infections
- These compounds are incorporated into the DNA strand, fragment the DNA thus preventing the synthesis of DNA and RNA
- These compounds also lead to the formation of free radicals, which can damage DNA and cell membranes

Cytotoxic Chemotherapeutic Agents: Antibiotics

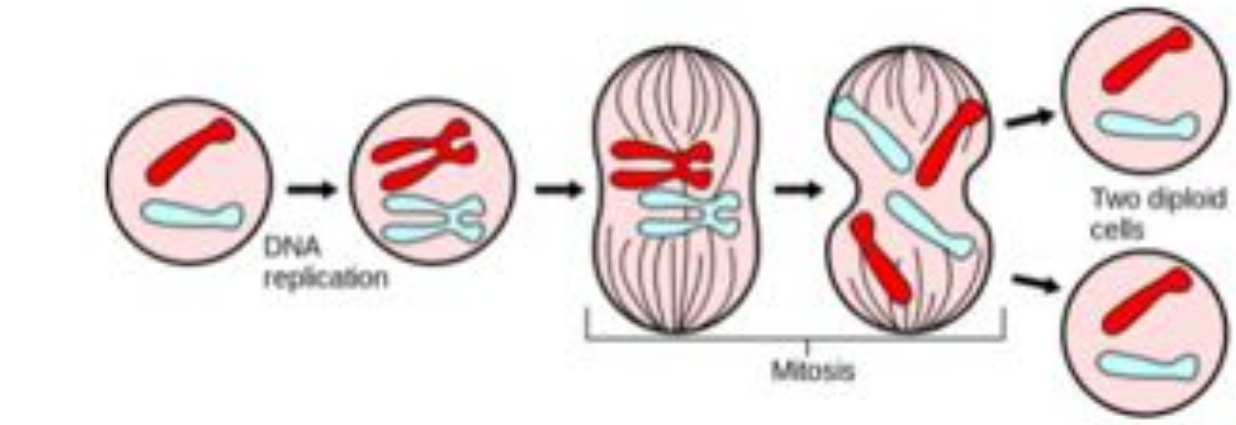
- Fungal in origin
- Examples
  - doxorubicin (Adriamycin) — Cardiomyopathy: CHF
  - daunorubicin (DaunoXome) — Myelosuppression, cardiomyopathy
  - Bleomycin (Blenoxane) — Myelosuppression, pulmonary damage
  - Mitomycin C
- Used to treat testicular, hematologic cancers and sarcomas, breast cancer

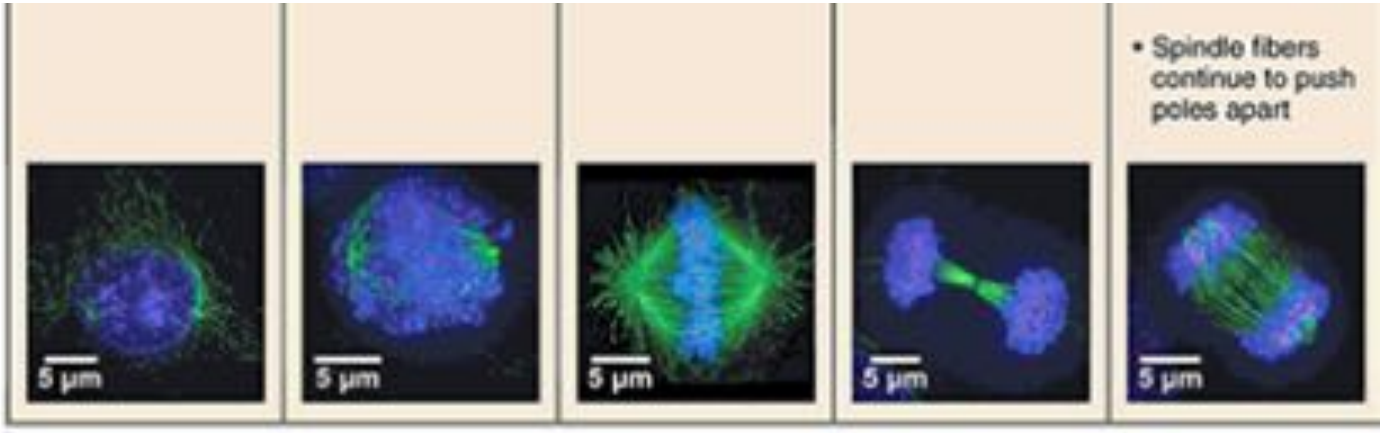
Cytotoxic Chemotherapeutic Agents: Antibiotics

- Anthracyclines:
  - Daunorubicin
  - Doxorubicin (Adriamycin)
  - Doxorubicin liposomal
  - Epirubicin
- Can permanently damage the heart if given in high doses.
- Often have lifetime dose limits

Cytotoxic Chemotherapeutic Agents: Mitotic Inhibitors

- Are derived from natural products such as plants
- They interfere with the formation of the mitotic spindle, subcellular structures that transfer genetic material from the mother cell to the two daughter cells.
- When the cell attempts to divide, the nuclear material becomes disrupted and is dispersed throughout the cytoplasm





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Mitotic Inhibitors: Plant Alkaloids

- Vinca alkaloids-derived from the periwinkle plant

Vinblastine	Neurotoxicity
Vincristine	Neurotoxicity, neuromyopathy
Paclitaxel (Taxol)	Myelosuppression, neuromyopathy

- Used to treat hematologic, lung and breast cancers

Mitotic Inhibitors: Topoisomerase inhibitors

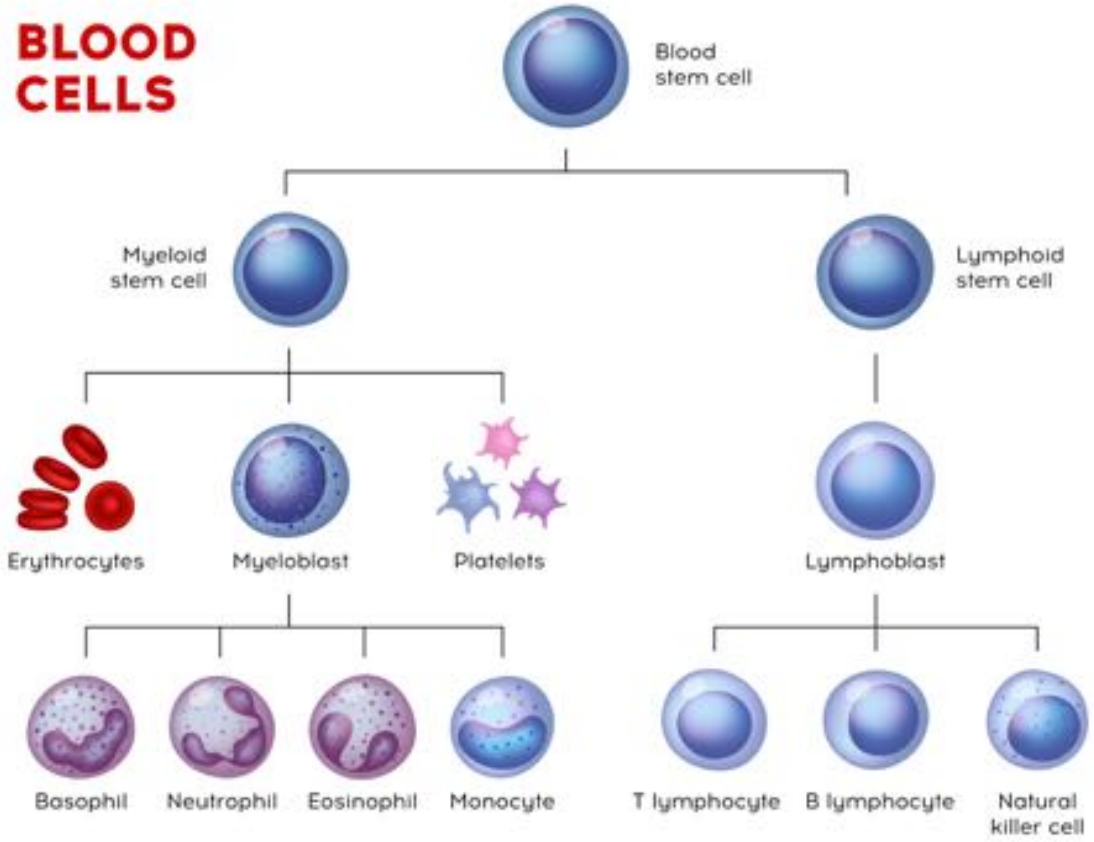
- Interfere with enzymes called topoisomerases, which help separate the strands of DNA so the strands can be copied
- Irinotecan
- Irinotecan liposomal
- Topotecan
- Etoposide (VP-16)

Periwinkle flowers in the garden [Used by permission]

White Blood Cells

- Made in the Marrow, found in the blood, lymph and various tissues
- Are a part of the body's immune system
- Types of WBCs
  - Granulocytes: Neutrophils, Eosinophils, and Basophils
  - Lymphocytes

White Blood Cells



Types of Immunotherapy

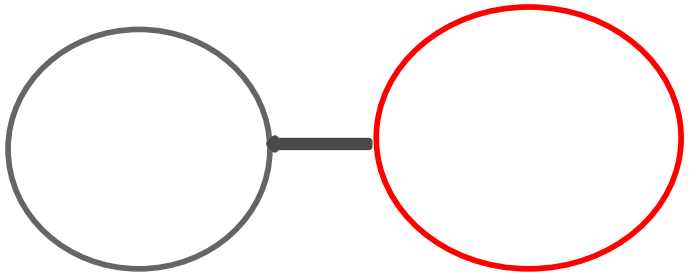
- Immune Checkpoint Inhibitors
- Monoclonal antibodies
- Vaccines
- Immune System Modulators
- T-cell transfer therapy
- Hormones
- Target Therapies

Immune Checkpoint Inhibitors

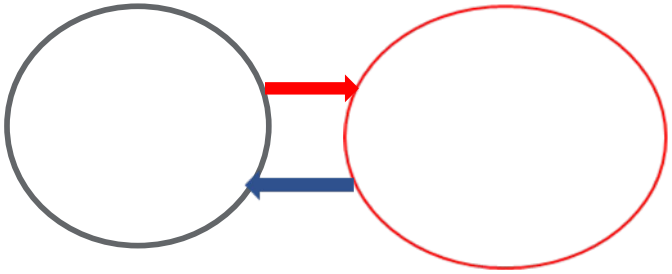
- Immune cells, particularly T-Cells, have cell surface proteins which, when stimulated, dampen immune responses i.e. act like a brake
- These proteins are called checkpoints
- Immune checkpoint inhibitors
  - Drugs which inhibit these checkpoints, allow immune cells to respond more strongly and to attack cancer cells more aggressively
  - Used against a large number of solid tumors

Immune Checkpoint Inhibitors

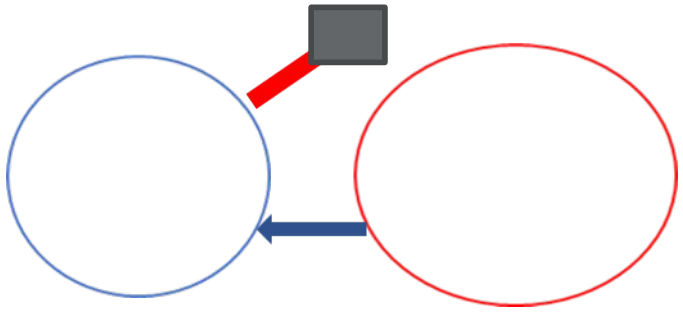
Cancer Cells T-Cells



Initiation of Immune response to the presence of a cancer cell



Cancer cell linked to a T-cell which acts to slow or eliminate the T-cell response to the cancer cell



Action of a checkpoint inhibitor disrupts the cancer cell's link to the T-Cell allowing immune response to move forward

Q6

Immune Checkpoint Inhibitors

- Examples of immune checkpoint inhibitors
  - Pembrolizumab (Keytruda)-melanoma and lung cancer
  - Nivolumab (Opdivo)-Lung Cancer, kidney cancer, bladder cancer, melanoma, kidney
  - Cemiplimab (Libtayo)- squamous cell carcinoma

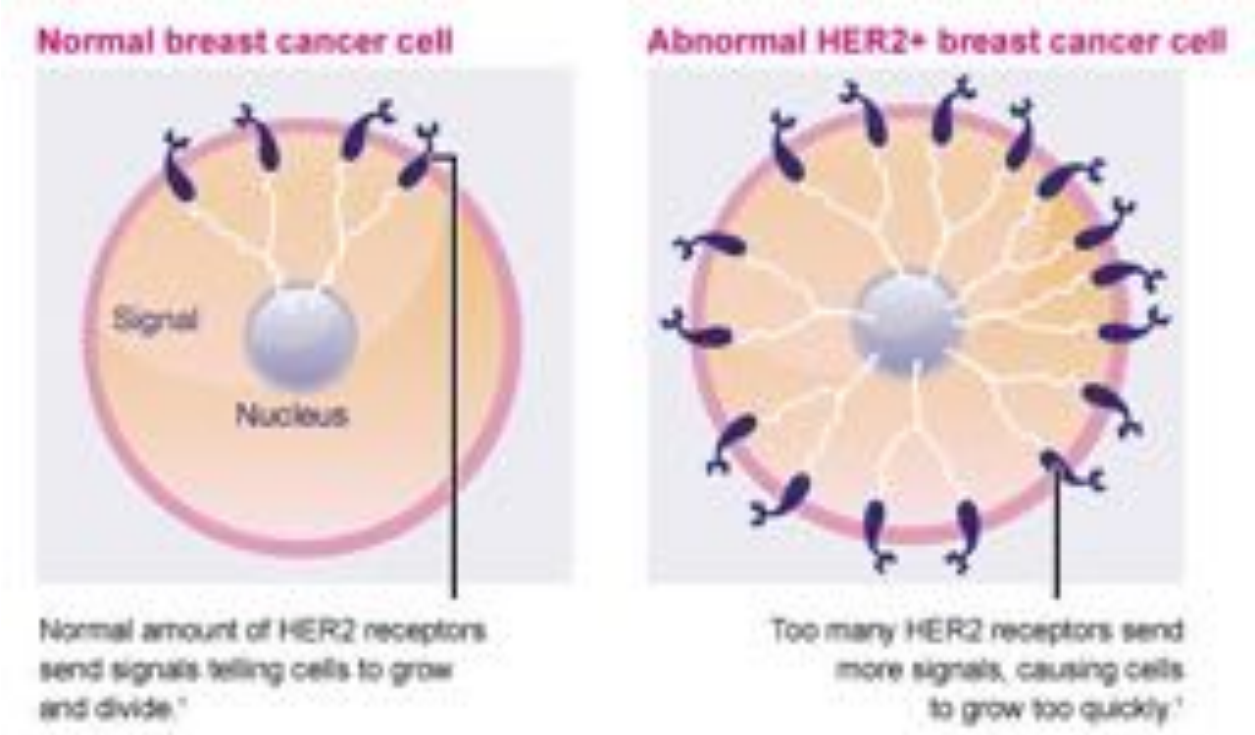
Monoclonal Antibodies

- Monoclonal antibodies are identical immunoglobins (antibodies) that are specific for a single antigen.
- Nivolumab (Opdivo) is a monoclonal antibody
  - Checkpoint inhibitor
- alemtuzumab (Campath)
  - Used to treat chronic lymphocytic leukemia (CLL)
  - Binds to CD52, an antigen found on the surface of normal and malignant lymphocytes
  - Also used to treat MS

Monoclonal Antibodies

- Trastuzumab (Herceptin)
  - Used to treat breast cancer patients that are HER2 receptor positive
  - HER2 receptors found on the cell surface of breast cells and promotes cell growth when activated
  - In some patients with breast cancer, cells have too man of these receptors ⟶ excessive cell growth
  - This monoclonal antibody binds to HER2 receptor causing internalization and downregulation of HER2 receptors thus limiting growth

Monoclonal antibody: Herceptin



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Monoclonal Antibodies

- Rituximab (Rituxan) Used to treat leukemias and lymphomas
  - Rituximab (Rituxan
  - This antibody attaches to a surface protein on blood cells called CD20. Binding leads to the destruction of these cells.
  - Used to treat patients who have malignant B cells with CD20 on their surfaces

Immune System Modulators

- A type of immunotherapy that enhances the body's immune response against cancer
  - Interferons: Enhances the immune response to cancer cells by increasing the activity of T-cells or slowing the growth of tumor cells
  - Interleukins: A group of cytokines
  - They increase the number of T- and B- cells in the body

Immune System Modulators

- Thalidomide (Thalomid®)
  - Acts to stimulate T-cells
  - Has anti-angiogenesis properties
  - Used to treat multiple myeloma and graft vs. host disease
  - Adverse effects include: blood clots, neutropenia, pulmonary hypertension, birth defects
  - History of Thalidomide

Vaccines

- Vaccine against Human papillomavirus (HPV)
  - H Papillomavirus Vac (Gardasil)
  - Has been linked to cervical, anal, throat, vaginal, vulvar, and penile cancers
  - Vaccine, when given to children and certain young adults, helps protect against all cancers associated with this virus
- Sipuleucel-T is used to treat men with metastatic prostate cancer

T-Cell Transfer Therapy

- CAR-T
  - T-cells are harvested from the patient
  - These cells are engineered to target a specific protein i.e. specific to a cancer cells
  - These modified T-cells are grown up in the lab and then infused into the patient
  - Used to treat non-Hodkins lymphoma

Hormone Therapies

- The surface membranes of some breast cancer cells have receptors specific for hormones, like estrogen and progesterone.
- The binding of these hormones to their receptors stimulate growth of the cancer cells
- Treatments that stop hormone binding can limit cancer cell growth

Hormone Therapies Breast Cancer

- 2 out of 3 breast cancers are estrogen receptor positive
- Estrogen/progesterone can increase cancer growth.
- Tamoxifen
  - Drug that blocks estrogen/progesterone receptors
  - May be given after surgery and XRT

Hormone Therapy Breast Cancer

- Aromatase inhibitors (AI):
  - Lower in vivo estrogen levels
  - Letrozole (Femara)
  - Anastrozole (Arimidex)
  - Exemestane (Aromasin)
- Adverse effects
  - Muscle pain and joint stiffness and/or pain

Hormone Therapy- Prostate Cancer

- Androgen deprivation therapy (ADT)
  - Prostate cancer
  - Androgens can fuel tumor growth
  - Goal is to reduce the amount of androgens in the body
  - Luteinizing hormone-releasing hormone (LHRH) agonists
  - LHRH antagonist
  - Adverse effects:
    - ED
    - Loss of muscle mass/weakness
    - Weight gain

Targeted Therapies

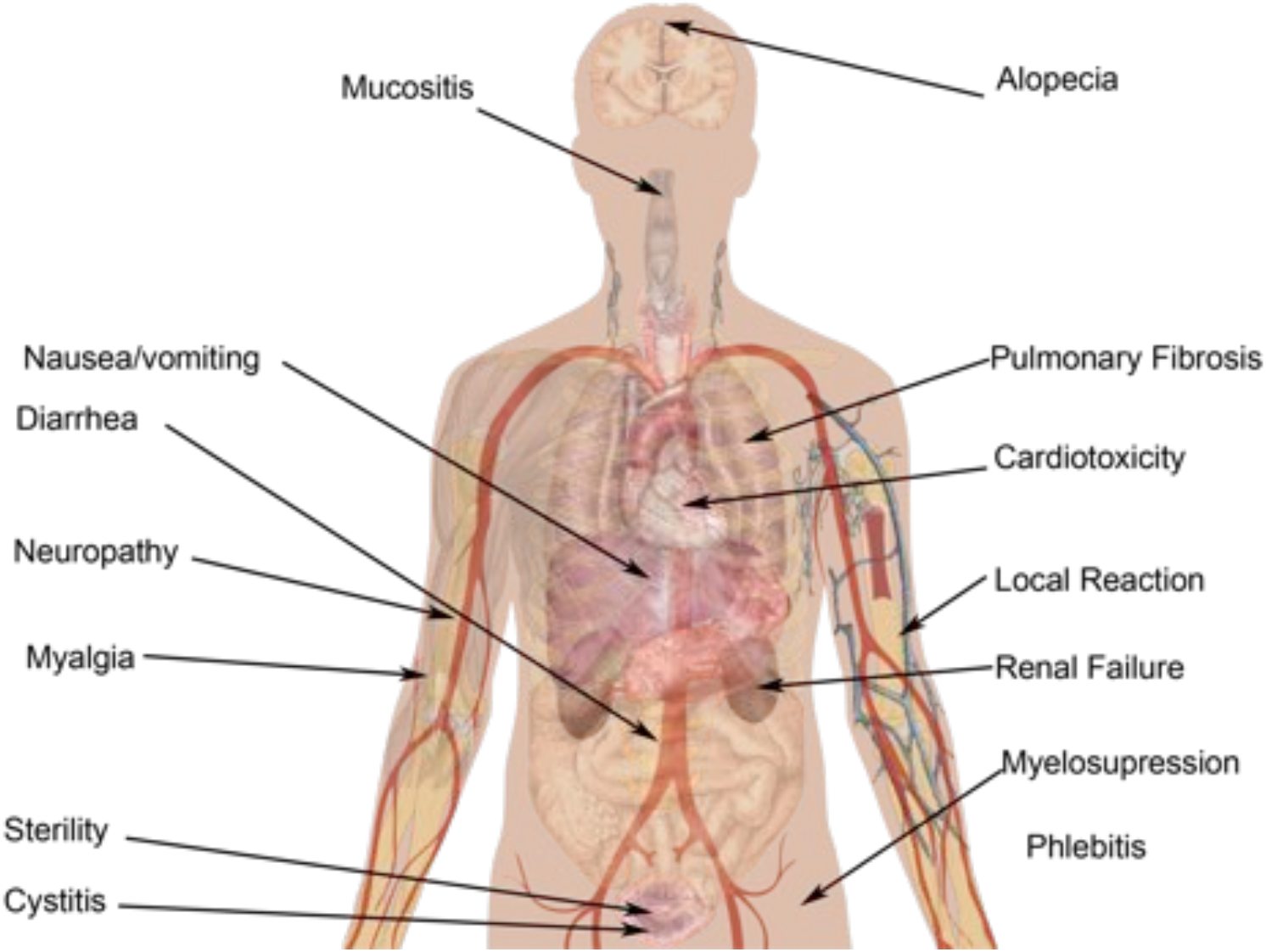
- These are chemical entities that preferentially target a protein or enzyme that carries a mutation or other genetic alteration that is specific to a cancer cell and not found in normal host tissue.
- Blocking these specific molecules stops growth of cancer cells
- Many are monoclonal antibodies

Targeted Therapies

- Many specific targeted therapies act by inhibiting molecules that regulate cell growth
  - Tyrosine kinase inhibitors
- Velcade (Bortezomib)
  - It appears to facilitate apoptotic degradation of multiple myeloma cells by inhibiting factors that inhibit apoptotic pathways.

CHEMOTHERAPEUTIC AGENTS: Implications for Rehabilitation Specialists

ADVERSE EFFECTS



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Treatment Adverse Effects: Cardiac

- Anthracyclines are not the only cardiotoxic chemotherapeutic agents
  - All “traditional” chemo drugs carry risk for cardiac damage
  - Targeted therapies carry risk for cardiac damage
    - Herceptin and Avastin
    - Velcade
    - Gleevec
  - Yeh & Bickford. JACC. 2009;53:2232

Adverse Effect Classification - Temporal Scheme

Onset	Time Frame	Adverse Effect
Immediate	Occurs within thirty minutes of administration	Venous pain Facial/body flushing Cardiac Arrhythmias Hypotension Hypersensitivity Anaphylaxis Hemorrhagic cystitis Abnormal tastes and smells Mucositis

Adverse Effect Classification - Temporal Scheme

Onset	Time Frame	Adverse Effect
Short to Medium	Occurs within hours and up to seven days of administration	Discoloration of urine Tumor lysis syndrome Nausea and vomiting Mucositis CNS Toxicity Anorexia Fatigue Constipation Diarrhea

Adverse Effect Classification – Temporal Scheme

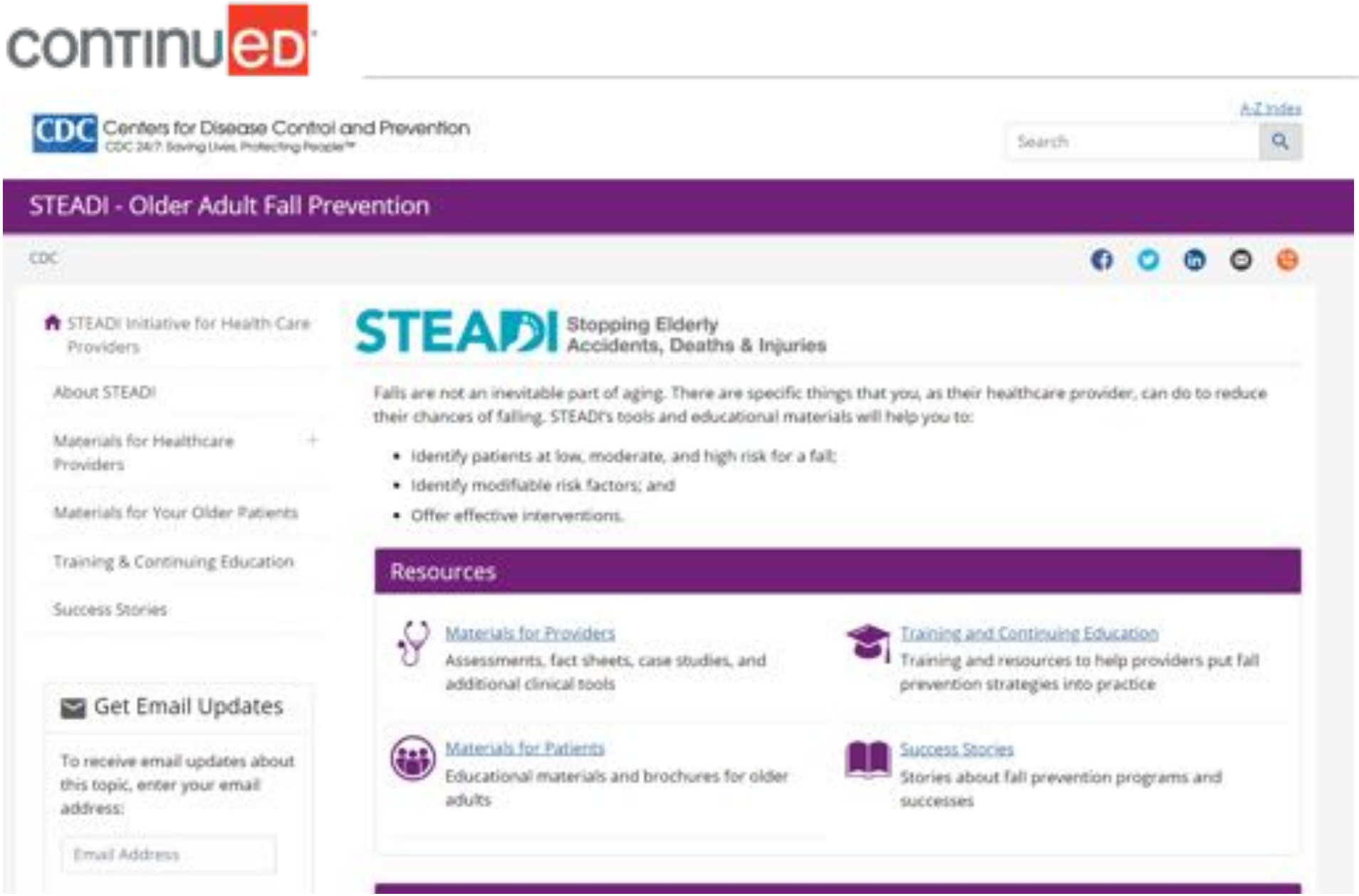
Onset	Time Frame	Adverse Effect
Long term or late or latent	Occurs within hours and up to seven days of Administration. Some adverse effects may continue after treatment completed or appear months and years after completion of treatment	Bone Marrow depression Alopecia Liver dysfunction Renal toxicity Cardiac toxicity Peripheral neuropathy Pulmonary Fibrosis Changes in fertility

Balance and Falls – Fall Risk

- Breast cancer survivors (age <70 years) s/p chemotherapy, + or - hormone therapy
  - 75% had >1 fall over 18 months, vs. 45% in the healthy control group
- Prostate cancer survivors (age >70 years) receiving androgen deprivation therapy
  - 22% had >1 fall over 3 months, vs. 6% to 9% in general elderly populations
- Bylow 2008, Winters-Stone 2009, Stone 2011

Balance and Falls: Consequences

- Increased likelihood of:
  - Hematomas
  - Neurologic injury
  - Fractures
  - Bleeding events
  - Possibly reduce overall survival
- Added symptom burden:
  - delay delivery of cancer treatments resulting in altered care, and possibly worsening the course of the disease or prognosis



https://www.cdc.gov/steadi/

Frailty

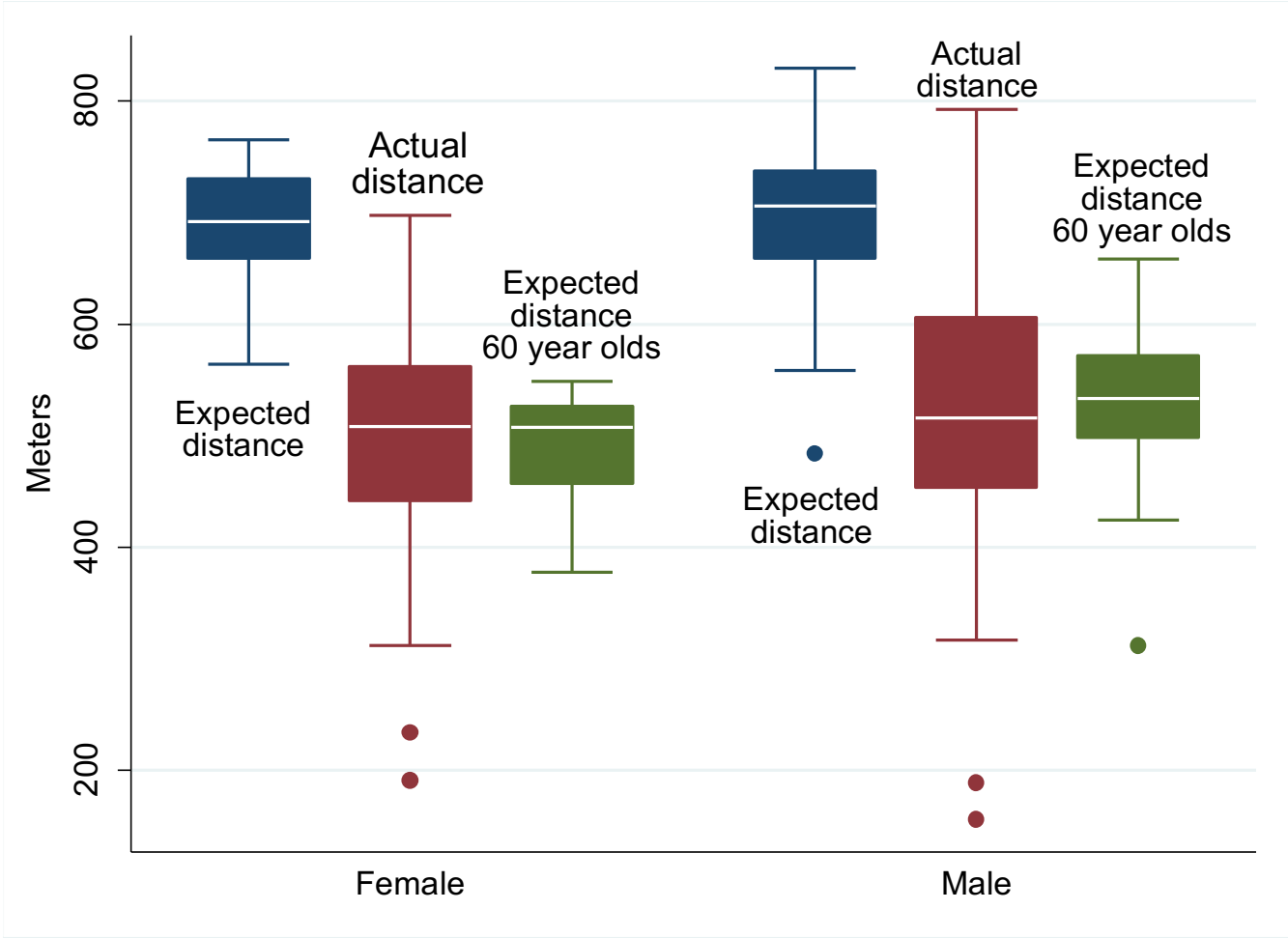
- Frailty: a state of vulnerability to poor restoration of homeostasis following a stressor event
- Loss of physiologic reserve
- Present in 10% of those over 65
- Present in 50% of those over 85
- Because cancer is a disease of aging, one might expect frailty to be present before chemotherapy begins and after chemotherapy has been completed

Frailty

- Characteristics
  - Unintentional weight loss
    - >10 pounds in prior year
    - > 5% of body weight in prior year
  - Weakness
    - Grip strength in the lowest 20% at baseline
  - Poor endurance/fatigue
  - Slowness
    - Gait Speed (slowest 20% of the population)
  - Inactive

  - Fried et al. J Gerontol A Biol Sci Med Sci (2001) 56 (3): M146

Frailty Phenotype/Characteristics



Provided by K.K. Ness

Frailty Questionnaire

- F (Fatigue): Are you fatigued? Y/N
- R Cannot walk up a flight of stairs Y/N
- A Cannot walk 1 block Y/N
- I Do you have > 5 illnesses Y/N
- L Have you lost more than 5% of your weight in the past 6 months Y/N
- Short physical performance Battery
- Van Kan A. et al. J Nutr Health Aging 2008;12(1):29–37

Frailty

- Meta analysis
- Incidence of frailty
  - 13-68%
- Outcomes of frailty
  - Increased risk for all cause mortality, postoperative mortality chemotherapy intolerance and post-operative complications
  - Possible increased risk for chemotherapy related side effects
  - Handforth C, et al Annals of Oncology. 2015;26:1091

Frailty and Physical Therapy Implications

- Evaluations should include a frailty assessment as part of an evaluation
- Therapeutic interventions can improve strength, endurance and gait speed
  - Dent E, et al. Lancet. 2019 Oct 12;394(10206):1376-1386
- Physical therapy interventions can be administered:
  - Pre-treatment
  - During treatment
  - Post treatment
- Marzetti E, et al. Aging Clin Exp Res . 2017 Feb;29(1):35-42.

Treatment Adverse Effects: Cardiac

- Anthracyclines Doxorubicin (Adriamycin)
- Very effective chemotherapeutic agent
  - Adverse cardiac effects appear immediately or upwards of 20-30 yrs. down stream of treatment.
  - Results in congestive heart failure (CHF)
- Review contraindications for exercise (AHA or ACSM)
- Intervention: Reconditioning
- Cattadori G., et al. ESC Heart Fail. 2018;5:222-232

Skeletal Muscle Damage

- Whole muscle dysfunction
  - Decreased strength
  - Decreased muscle mass
  - Christensen JF et al. Annals of Oncol. 2014;25:947
- Muscle cell dysfunction
  - Reduced mitochondrial density
  - Reduced cross bridge kinetics
  - Toth MJ, et al. J Appl Physiol. 2013;114:858.

References

- Please download pdf file.