PHARMACOLOGY 101:
MECHANISM AND TARGETS IN MEDICAL ONCOLOGY

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Objectives

- To define the purposes of cancer therapy
- To describe the differences among cancer therapies
- To have a basic understanding of the mechanisms of actions of chemotherapy, hormone therapy, targeted therapies, and immunotherapy
- To have a basic understanding of common toxicities for cancer treatments
- To have an understanding of available resources for information regarding cancer therapies
Cancer treatment
Cancer therapy

• Cure
  • No evidence of disease (NED)

• Control
  • Prolong length and quality of life, prevent distant and possible unknown metastases
  • Cure is not realistic

• Palliation/Comfort
  • Symptom management, improve comfort and quality of life
  • Appropriate when cure and control are not feasible

• Systemic Treatment types
  ➢ PO, IV, IM, SQ, IT

• Combination therapy

• Treatment considerations
  • Neoadjuvant
  • Adjuvant
  • Induction
  • Maintenance
  • Metastatic
  • Radio sensitizer
Cancer Therapy Agents

- Chemotherapy
- Hormonal Therapy
- Immunotherapy
- Therapeutic Antibodies
- Antibody-Drug Conjugates
- Kinase Inhibitors
- Other
Common Cancer Therapy Side Effects

- Fatigue
- Myelosuppression
- Nausea/Vomiting
- Diarrhea/Constipation
- Mucositis
- Peripheral Neuropathy
- Alopecia
- Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies and rash
- Oncology Emergencies
Cancer Therapy Limitations

- Toxicity of agents
- Lifetime dose
- Hypersensitivity reactions
- Drug resistance
- Secondary malignancies
- Adherence
- Insurance Authorization
- Patient cost
Chemotherapy

- Treatment of cancer cells with chemicals
- Cytotoxic-poisonous to cells
# Chemotherapy

<table>
<thead>
<tr>
<th>Phase cycle specific agents</th>
<th>Cell cycle specific agents</th>
<th>Cell cycle non-specific agents</th>
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<tbody>
<tr>
<td>Only the cells in a specific cycle are affected dividing throughout cycle</td>
<td>Effects are mostly on the cells actively</td>
<td>Effects are on cells at any phase</td>
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Chemotherapy Classifications

- Alkylating Agents
- Antimetabolites
- Antimicrotubule Agents
- Topoisomerase I Inhibitors
- Topoisomerase II Inhibitors
- Antibiotic Oncologics
- Asparaginase derivatives
- Hypomethylating Agents
- Other
Alkylating Agents

- Mechanisms of action: Interfere with DNA replication through cross linking of DNA strands, DNA strand breaking, and abnormal base pairing of proteins
- Most agents are cell cycle nonspecific
- Activated by cytochrome p450
- Toxicities: Nausea/Vomiting, Hematopoietic, Reproductive
Alkylating Agents

- Alkyl sulfonates
  - busulfan; CML, Myelofibrosis

- Ethyleneimines
  - thiotepa; Breast, Ovarian

- Nitrogen mustards
  - bendamustine; Given IV; CLL, NHL
  - chlorambucil; HL, NHL, CLL
  - cyclophosphamide; Given IV or PO
    - HL, NHL, MM, CML, AML, Breast
  - ifosfamide; Testicular, Sarcoma
  - melphalan; MM
Alkylating Agents

- Nitrosoureas
  - Most agents cross blood-brain barrier
  - carmustin; Brain, MM, HL, NHL
  - lomustine; oral agent: Brain, HL, NHL
  - streptozotocin; Pancreatic
Alkylating Agents

- Platinum Analogues
  - cisplatin-heavy metal; Testicular, Ovarian, Bladder, Lung
  - carboplatin-2nd generation platinum analogue; Solid tumors
  - oxaliplatin-3rd generation platinum analogue; Colorectal

- Triazenes
  - dacarbazine; HL, Melanoma
  - temozolomide; Brain
Alkylating Agents

- Other
  - procarbazine; HL
Antimetabolites

- Mechanism of action: Inhibit DNA synthesis by substituting metabolites or structural analogues during DNA synthesis.
- Most agents are **phase cycle specific**.
- Toxicities: Hematopoietic and GI.
- Folate Analogs, Purine Analogs, Pyrimidine Analogs, Other.
Antimetabolites

- **Folate Antagonists**
  - methotrexate; Breast, Osteosarcoma, H/N
  - pemetrexed; Lung, Mesothelioma
  - pralatrexate; Peripheral T-cell lymphoma
Antimetabolites

- **Purine Antagonists**
  - cladribine; Hairy Cell Leukemia
  - fludarabine phosphate; CLL

- **Pyrimidine Antagonists**
  - 5 fluorouracil - GI malignancies
  - capecitabine - oral agent; GI, Breast
  - cytarabine; AML
  - fluorouracil; GI, Pancreatic, Breast
  - gemcitabine; Pancreatic, breast, ovarian, Lung
Antimetabolites

- Other
  - hydroxyurea-oral agent; P vera, thrombocytopenia, H/N
Antimicrotubule Agents

- Mechanism of action: Block cell division by preventing microtubule function
- Plant derived
- Toxicities: Peripheral Neuropathy
Antimicrotubule Agents

- Epothilones
  - ixabepilone; Breast

- Halichonrin B analogue
  - eribulin mesylate; Breast, Liposarcoma

- Taxanes
  - paclitaxel; Breast, Ovarian, Lung, Sarcoma
  - albumin-bound paclitaxel; Breast, Pancreatic, Lung
  - cabazitaxel; Prostate
Antimicrotubules

- Vinca Alkaloids
  - vinblastine; HL, Testicular
  - vincristine; HL, NHL, ALL, Solid tumors
  - liposomal vincristine; ALL
  - vinorelbine; Lung, Breast
Topoisomerase I Inhibitors

- Mechanism of action: Interferes with the activity of topoisomerase in the process of DNA replication
- Toxicities: Nausea, vomiting, diarrhea, abdominal cramping.
Topoisomerase I Inhibitors

- Camptothecin derivatives
  - irinotecan; Colorectal
  - irinotecan liposome; metastatic pancreatic
  - topotecan; Ovarian, Lung, Cervical
Topoisomerase II Inhibitors

• Mechanism of action: Interferes with the activity of topoisomerase in the process of DNA replication
• Toxicities: Nausea, vomiting, diarrhea, bone marrow suppression
Topoisomerase II Inhibitors

• Anthracyclines
  • daunorubicin; ALL, AML
  • doxorubicin; baseline EF, lifetime cumulative dose; Breast, Sarcoma
  • liposomal doxorubicin; Ovarian, Kaposi sarcoma
  • epirubicin; Breast
  • idarubicin; AML

➢ Epipodophyllotoxins
  • etoposide; Lung, Testicular
Antibiotic Oncologics

- **Mechanism of action:** DNA intercalation (insert between two strands of DNA), generate highly reactive free radicals that damage intercellular molecules
- **Toxicities:** Bone marrow suppression
- **Antitumor antibiotics**
  - Bleomycin; Pulmonary toxicities; Lung, Testicular, NHL
  - Mitomycin; Delayed bone marrow suppression; Anal, Pancreatic, Stomach
Antibiotic Oncologics

• Mechanism of action: DNA intercalation (insert between two strands of DNA), generate highly reactive free radicals that damage intercellular molecules

• Toxicities: Bone marrow suppression
Asparaginase Derivatives

- Mechanism of action: Catalyzes asparagine deamination resulting in decreased circulating asparagine and cytotoxicity of asparagine-dependent leukemic cells
- Toxicities: Hypersensitivity reaction, hyperglycemia
Aspariginase Derivatives

- **Mechanism of action:** Catalyzes asparagine deamination resulting in decreased circulating asparagine and cytotoxicity of asparagine-dependent leukemic cells.
- **Toxicities:** Hypersensitivity reaction, hyperglycemia.
- E. coli derived asparaginase; ALL
- Pegaspargase; ALL
Hypomethylating Agents

- Mechanism of action: Produces DNA hypomethylation restoring normal tumor suppressor gene function and control of cellular differentiation and proliferation
- Toxicities: Bone marrow suppression
Hypomethylating Agents

- Mechanism of action: Produces DNA hypomethylation, restoring normal tumor suppressor gene function and control of cellular differentiation and proliferation.

- Toxicities: Bone marrow suppression
  - azacitidine; MDS
  - decitabine; MDS
Other Chemotherapy

- Other
  - arsenic trioxide; causes apoptosis-like changes to NB4 human promyelocytic leukemia cells in vitro; APL
  - trabectedine; binds and alkylates DNA in the minor groove leading to disruption of the cell cycle and eventual cell death; Liposarcoma, Leiomyosarcoma
  - octreotide; inhibits multiple hormones including growth hormone, glucagon, insulin and LH; Carcinoid tumors, diarrhea
Hormonal Therapy

Used in managing hormonally sensitive cancers (Breast, Prostate, Ovarian, and Endometrial cancer)

Mechanism of action: The hormone changes the hormonal environment that alters growth factors thus the stimulus for tumor growth is suppressed or removed
## Hormone Therapy

### Women
- Fatigue
- Hot flashes
- Mood swings
- Nausea
- Osteoporosis
- Weight gain

### Men
- Decreased sexual desire
- Enlarged breasts
- Hot flashes
- Impotence
- Incontinence
- Osteoporosis
Examples of Hormonal Therapy

- Androgen receptor antagonists
- Aromatase Inhibitors
- Estrogen receptor antagonist
- Selective estrogen receptor modulator (SERM)
- LH-RH (GnRh) analogues and antagonists
- Other
Androgen Receptor Antagonists

- Mechanism of action: Binds and inhibits androgen receptors
  - bicalutamide; Prostate
  - flutamide; Prostate
  - enzalutamide; Prostate
Aromatase Inhibitors

- Mechanism of action: lowers the amount of estrogen which signals hormone receptors.
- Slows tumor growth by inhibiting this process.
- Used in post-menopausal women with hormone receptor positive breast cancer.
- Toxicities: Arthralgia, vaginal dryness, accelerated bone loss.
- letrozole; Breast
- exemestane; Breast
- anastrozole; Breast
Estrogen Receptor Antagonist

- Mechanism of action: Binds to estrogen receptors and down regulates estrogen receptor protein producing anti-estrogenic effects
- Toxicities: Injection site pain, hot flashes, arthralgia
- fulvestrant; Breast
Selective Estrogen Receptor Modulator (SERM)

- Mechanism of action: Selectively binds to estrogen receptors producing anti-estrogenic effects
- Toxicities: Hot flashes, vaginal dryness
- tamoxifen; Need baseline GYN exam; Breast, premenopausal
- raloxifene; Post menopausal high risk for invasive breast cancer
Luteinizing Hormone-
Releasing Hormone

• Agonists
  • Suppress secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from pituitary gland thus decreasing testosterone levels

• Antagonists
  • Works on the gonadotropin releasing hormone
Luteinizing Hormone-Releasing Hormone Agonists

- leuprolide
  - Gonadotropin-releasing hormone (GnRH) agonist
  - Indicated for prostate cancer
- goserelin
  - Indicated for advanced breast and prostate cancers
- triptorelin
  - Indicated for ovarian and prostate cancers
Other Hormonal Agents

- abiraterone; inhibits 17 alpha-hydroxylase/C17,20-lyase to block androgen biosynthesis leading to decreased androgen-sensitive tumor growth; Prostate
- megestrol acetate; agonizes glucocorticoid receptors; Cancer related anorexia
- ketoconazole-inhibits fungal cell membrane ergosterol synthesis; Prostate
IMMUNOTHERAPY: Using the Body To Fight Cancer
Immunotherapy

- Also called Biological Response Modifier Therapy
- Stimulate or restore immune system to fight cancer cells
- Modify the relation between the tumor and the host
- Includes antibodies, cytokines, and other substances that stimulate immune function
Immunotherapy

Types

- ipilimumab: binds to CTLA-4 antigen to block activity and augment T-cell activation and proliferation; Melanoma
- nivolumab: binds to PD-1 receptor on T-cells blocking PD-1 pathway mediated anti-tumor immune response inhibition; Metastatic NSCLC, Metastatic Melanoma, Renal cell carcinoma, Squamous cell H/N, Classic HL, Urothelial, MSI-H (microsatellite instability-high) or dMMR (mismatch repair deficient met. Colorectal cancer

Interferon, interleukins, anti-CTLA4, anti-PD-1, anti-PDL-1, cancer vaccines
Immunotherapy

**pembrolizumab**: binds to PD-1 receptor on T-cells blocking PD-1 pathway mediated anti-tumor immune response inhibition; Melanoma, NSCLC, HNSCC, Classical HL, Urothelial/Bladder

**durvalumab**: blocks PD-L1 with the PD-1 and CD80 molecules; recombinant DNA technology in Chinese Hamster Ovary cell suspension culture; Urothelial

**atezolizumab**: binds to PD-L1 and blocks interactions with both PD-1 and B7.1 receptors; Urothelial.
Immunotherapy

elotuzumab; humanized monoclonal antibody targeting SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7) protein; activates NKC through both the SLAMF7 pathway and Fc receptors; Multiple Myeloma

sipuleucel-T; Induces T-cell mediated immune response targeted against prostatic acid phosphate antigen; Prostate

tolimidone laherparepvec; Replicates within tumor and produces GM-CSF inducing tumor cell death and enhancing antitumor immune response; genetically engineered oncolytic virus; Given in divided doses to the tumor lesions in Melanoma
Interferon

Mechanism of action: Antiviral (inhibits viral replication), antiproliferative, and immunomodulatory effects, activate and increases cytotoxicity of natural killer cells, enhances immune response

Cytokines

Alpha, beta, and gamma derivatives

interferon alfa 2b; Hairy cell leukemia, Melanoma, NHL, Hepatitis
Interleukins

Mechanism of action: Stimulates T-lymphocyte proliferation, enhances killer T-cell activity, stimulates and enhances natural killer cells

Cytokines

Produced by helper T-cells

aldesleukin; Renal cell, Melanoma
Colony Stimulating Factors

**Red Cell**
- darbepoietin alpha
- Epoetin alpha

**White Cell**
- filgrastim
- tbo-filgrastim
- pegfilgrastim
- sargramostim
Targeted Therapies

- Prevent/Block/Interrupt Cell Growth
- Cut off blood flow to tumor
- Target defects in the cancer cells
- Carry other drugs to a tumor
- Cause cell death (apoptosis)
- Make the cancer cells more receptive to the immune system
Therapeutic Antibodies

• Engineered antibodies produced by a single clone of cells that is specific for a given antigen
• Passive immunotherapy
• Names end in “mab”
Therapeutic Antibodies

- **Murine-mouse**
- **Humanized-human**
- **Human Anti-Murine Antibody (HAMA)**
- **Chimeric-part mouse/human**
- **Conjugated-a chemotherapy drug, radioactive particle, or toxin is connected to monoclonal antibody**
- **Unconjugated-monoclonal antibody without any drug, radioactive particle, or toxin attached**
Therapeutic Antibodies
Common Targets

- CD20
- CD52
- EFGR
- HER2
- PD 1
- PIGF
- VEGFA
Therapeutics Antibodies

- CD20
  - rituximab; NHL, CD20-positive CLL, RA
  - ibritumomab tiuxetan; NHL
  - ofatumumab; CLL
Therapeutic Antibodies

• EGFR (epidermal growth factor receptor)
  • panitumumab; Colorectal
  • cetuximab; Colorectal, Squamous H/N

• HER2
  • pertuzumab; HER2 positive Breast
  • trastuzumab; HER2 positive Breast, HER2 positive Gastric
Therapeutic Antibodies

- **PIGF (Phosphatidylinositol-glycan biosynthesis class F protein)**
  - ziv-afibercept; Colorectal

- **RNAKL (Receptor Activator of Nuclear Factor Kappa-B Ligand)**
  - denosumab; Solid tumor bone metastasis, hypercalcemia, Giant cell tumor of bone

- **VEGF (Vascular endothelial growth factor)**
  - bevacizumab; Colorectal, NSC Lung non squamous, GBM, Renal cell, Cervical, Breast
  - ramucirumab; Gastric, NSC lung, colorectal
Antibody-Drug Conjugates

- **CD30**
  - brentuximab vedotin; HL, Systemic anaplastic large cell lymphoma

- **HER2**
  - ado trastuzumab emtansine; HER2 positive breast
Kinase Inhibitors

- Mechanism of action: Enzyme inhibitor that blocks the action of one or more protein kinase which alters biological processes including but no limited to modulate cell function; Most names end in “nib”
- Toxicities: Vary based on target
Kinase Inhibitors

• BCR-ABL (Abelson murine leukemia viral oncogene)
  • nilotinib; Ph-positive CML
  • dasatinib; Ph-positive CML
  • bosutinib; Ph-positive CML

• ALK (anaplastic lymphoma kinase)
  • crizotinib; 1st generation ALK/ROS1 positive NSCLC
  • ceritinib; 2nd generation ALK positive NSCLC
  • alectinib; 3rd generation ALK positive NSCLC
  • brigatinib; ALK positive NSC Lung
Kinase Inhibitors

- BRAF
  - dabrafenib; Melanoma
  - vemurafenib; Melanoma
  - cobimetinib; in combination with vemurafenib; Melanoma
- BTK (Bruton’s Tyrosine Kinase)
  - ibrutinib; CLL, Mantle cell lymphoma
- CDK 4,6
  - palbociclib; ER/PR positive HER2 negative Breast
Kinase Inhibitors

- **EGFR (epidermal growth factor receptor)**
  - osimertinib; wild type sparing; NSC Lung with EGFR T790M mutations
  - afatinib; NSC Lung with EGFR exon 19 deletions or exon 21
  - erlotinib; NSC Lung with EGFR exon 19 deletions or exon 21, Pancreatic with gemcitabine
  - gefitinib; NSC Lung with EGFR exon 19 deletions or exon 21 mutations
Kinase Inhibitors

• FLT3 (FMS related Tyrosine Kinase 3)
  • sorafenib; Hepatocellular, Renal Cell, Thyroid
  • sunitinib (Sutent); Renal Cell, GIST, Pancreatic neuroendocrine
• BCL-2
  ➢ ventoclax; CLL with 17p deletion
    ➢ Restores apoptosis
Kinase Inhibitors

- HER2 (ERBB2/neu)
  - afatinib; NCS Lung with EGFR exon 19 deletions or exon 21 mutations
  - lapatinib; HER2 overexpressing Breast
- JAK 1/2
  - ruxolitinib; Myelofibrosis, Polycythemia vera
Kinase Inhibitors

- **KIT**
  - axitinib; Renal cell
  - regorafenib; Colorectal, GIST
  - dasatinib; Ph-positive CML, Ph-positive ALL
  - pasopanib; Renal cell, Soft tissue sarcoma
  - imatinib; Ph-positive CML
  - sunitinib; Renal cell, GIST
Kinase Inhibitors

- MEK (Mitogen-activated protein kinase)
  - trametinib; Melanoma
- mTOR (Mechanistic Target of Rapamycin)
  - sirolimus; Kidney transplant rejection prophylaxis
  - temsirolimus; Renal cell
  - everolimus; ER/PR positive HER2 negative Breast, Pancreatic neuroendocrine, Renal cell
Kinase Inhibitors

- idelalisib; inhibits P13K, disrupting B-cell receptor and cytokine signaling pathways, thus inhibiting malignant B-cell proliferation; CLL
Other Cancer Therapy

- PARP (poly (ADP-ribose) polymerase)
  - olaparib; BRCA-mutated Ovarian

- Proteasome
  - bortezomib; Multiple Myeloma, Mantle Cell Lymphoma
  - carfilzomib; Multiple Myeloma
  -Ixazomib; Multiple Myeloma

- omacetaxine mepesuccinate; inhibits protein synthesis; CML
Other Cancer Therapy

- Other
  - pomalidomide; Multiple Myeloma
  - lenalidomide; Multiple Myeloma, MDS, Mantle Cell Lymphoma
  - thalidomide; Multiple Myeloma
Supportive Care Medications

- IV hydration
- Electrolyte replacement
- Antiemetic's
- Antidiarrheal
- Stool softeners/laxatives
- Nutritional support
- Appetite stimulants
- Antidepressants/Antianxiety
## Advanced Practice Considerations

<table>
<thead>
<tr>
<th>Activity</th>
<th>Details</th>
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<tbody>
<tr>
<td>Maintain awareness of cancer agents and treatment options</td>
<td></td>
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<tr>
<td>Utilize Package Insert for drug details including dosing and toxicity management</td>
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<tr>
<td>Encourage supportive care to minimize toxicity</td>
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<tr>
<td>Collaborate with respective disciplines</td>
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<td>Support patients physically (symptom management), psychosocially (referrals to social work/case management), emotionally (referrals to psychology/support groups) and spiritually (refer to chaplain/spiritual counselor)</td>
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<td>Spend time with other team members</td>
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Resources

- chemocare.com
- uptodate.com
- Oncology Business Review
- ASCO
- American Cancer Society
  - 1-800-813-HOPE (4673)
  - http://www/cancer.org/
- National Cancer Institute
  - 1-800-4-CANCER (422-6237)
  - http://www.cancer.gov/
  - https://www.cancer.gov/about-cancer/treatment/drugs
- National Comprehensive Cancer Network
  - http://www.nccn.org/
- Vanderbilt My Cancer Genome
  - www.mycancergenome.org
Taking care of your mind & thoughts

Taking care of your physical health & body

Self-Care

Increasing your own well-being through self-care behaviors

Taking care of your spiritual health

Taking care of your emotions

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References

References