PHARMACOLOGY 101:

MECHANISM AND TARGETS IN MEDICAL ONCOLOGY

Lindsay Williamson

APRN, MSN, AOCNP

Biography

Lindsay Williamson is board certified as an Advanced Oncology Certified Nurse Practitioner as well as an Adult Nurse Practitioner. She received her BSN at West Chester University in West Chester, Pennsylvania and her MSN at La Salle University in Philadelphia, Pennsylvania. Lindsay has been an Oncology Nurse for 19 years with 11 of those years in the role of Nurse Practitioner. She has worked in a variety of settings including inpatient and outpatient as well as community based and academic based. Also, she has worked in a variety of roles including Oncology Staff Nurse, Infusion Nurse, ARNP in a community practice, Pharmaceutical Sales Representative and Clinical Operations Manager of the Lab Draw and Infusion areas at Moffitt Cancer Center. She is currently pursuing her DNP and teaching nursing students at St. Petersburg College and Pinellas Technical College.

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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


Simple 'n Easy
Pharmacology

Chemotherapy

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

Chemotherapy

Phase cycle specific agents

Only the cells in a specific cycle are affected dividing throughout cycle

Cell cycle specific agents

Effects are mostly on the cells actively

Cell cycle non-specific agents

Effects are on cells at any phase

Chemotherapy Classifications

- Alkylating Agents
- Antimetabolites
- Antimicrotuble Agents
- Topoisomerase I Inhibitors
- Topoisomerase II Inhibitors
- Antibiotic Oncologics
- Aspariginase 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
  - **<u>Most agents cross blood-brain barrier</u>**
  - 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, thrombocythemia, H/N

Antimicrotubule Agents

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

Antimicrotuble 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

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- Toxicities: Bone marrow suppression

Aspariginase Derivatives

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

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- 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

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- 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 grove 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

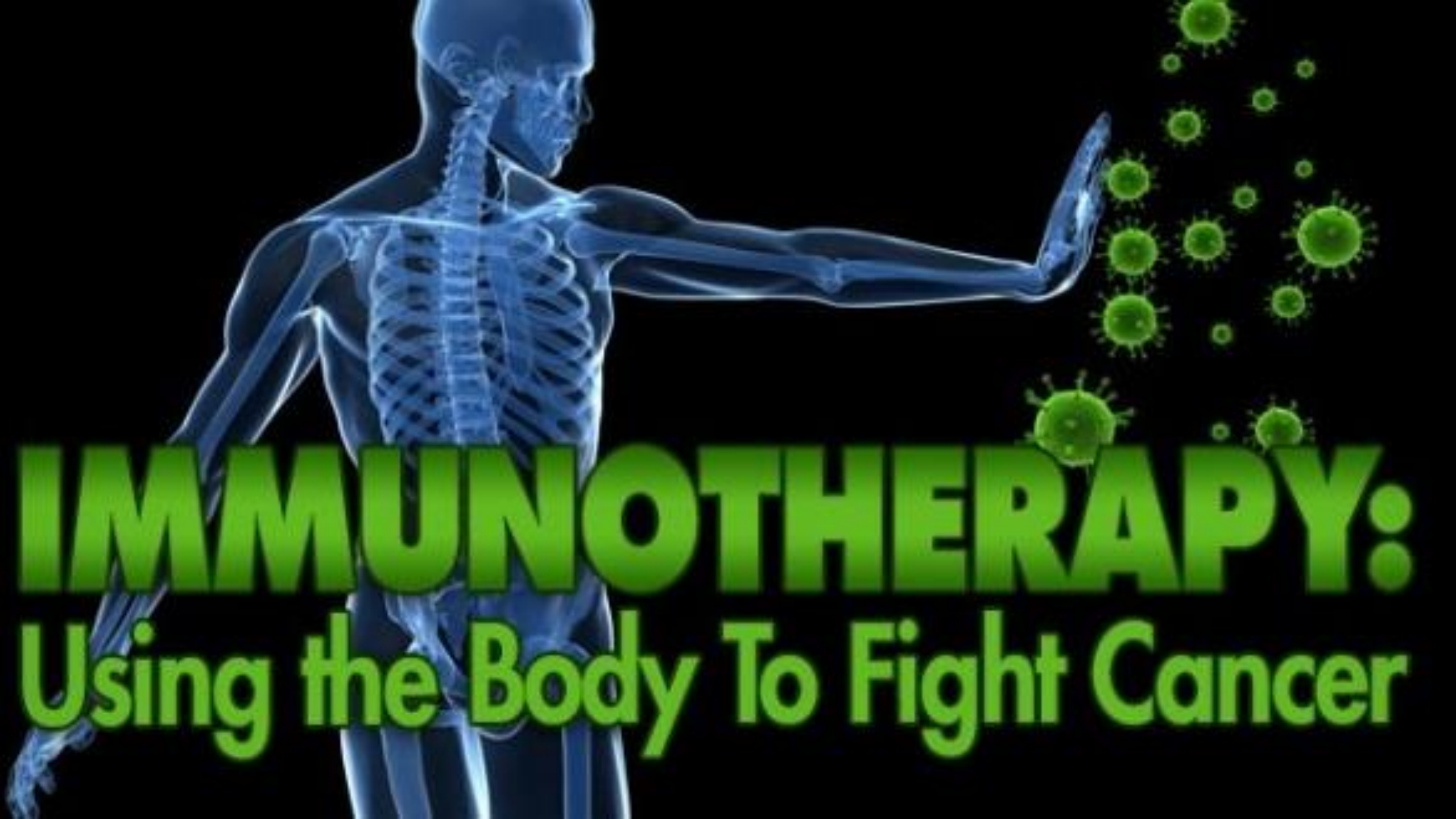
Luteinizing Hormone-Releasing Hormone Agonists

- 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


Google


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 (mismatche 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-filgrastin
pegfilgrastim
sargramostim

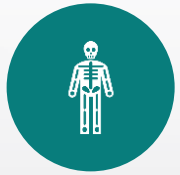

Prevent/Block/ Interrupt Cell Growth
Cut off blood flow to tumor
Target defects in the cancer cells
Carry other drugs to a tumor
Cause cell death (apoptosis)
Make the cancer cells more receptive to the immune system
Targeted Therapies

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 anaplatic 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, Polycythema vera

Kinase Inhibitors

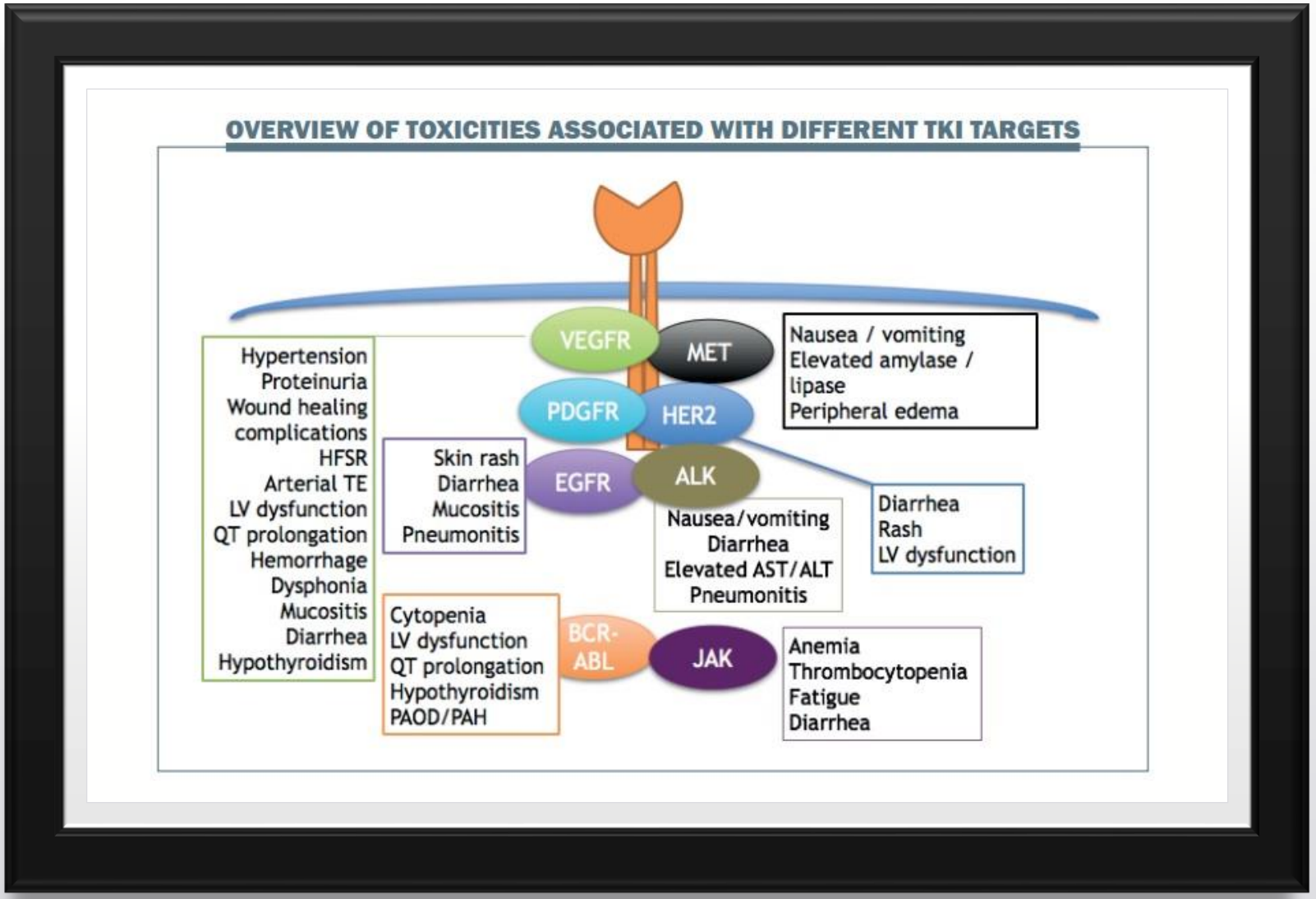
- KIT
  - axitinib; Renal cell
  - regorafenib; Colorectal, GIST
  - dasatinib; Ph-positive CML, Ph-positive ALL
  - pasopanib; Renal cell, Soft tissue sarcoma
  - imatinib; Ph-positive CML
  - sunitinib; Renal cell, GIST

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


OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS
VEGFR
MET
PDGFR
HER2
EGFR
ALK
BCR-ABL
JAK
Hypertension
Proteinuria
Wound healing complications
HFSR
Arterial TE
LV dysfunction
QT prolongation
Hemorrhage
Dysphonia
Mucositis
Diarrhea
Hypothyroidism
Nausea / vomiting
Elevated amylase / lipase
Peripheral edema
Skin rash
Diarrhea
Mucositis
Pneumonitis
Nausea/vomiting
Diarrhea
Elevated AST/ALT
Pneumonitis
Diarrhea
Rash
LV dysfunction
Cytopenia
LV dysfunction
QT prolongation
Hypothyroidism
PAOD/PAH
Anemia
Thrombocytopenia
Fatigue
Diarrhea

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

Maintain awareness of cancer agents and treatment options

Utilize Package Insert for drug details including dosing and toxicity management

Encourage supportive care to minimize toxicity

Collaborate with respective disciplines

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)

Spend time with other team members

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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