Principles of Cancer Therapy

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Objectives

• Describe genetic basis of carcinogenesis, the resulting hallmark characteristics of cancer and the basis for treatment with chemotherapy, targeted therapy, and immunotherapy.

• Discuss the pharmacological basis of targeted therapy in terms of targeting driver mutations, aberrant cell signaling, and the resulting side effects of targeted agents.

• Explain the interaction between the immune system and the cancer microenvironment with implications for the role of immunotherapy and the novel spectrum of side effects seen with the check point inhibitors.
History of Cancer Treatment

1950
1st chemotherapy agents approved: nitrogen mustards, chlorambucil, methotrexate

1960
Chemotherapy given as adjuvant therapy to prevent relapse

1970
Cancer causing oncogenes and tumor suppressor genes discovered

1980
1st monoclonal antibody based therapy approved

1990
1st targeted therapy approved

2000
Advent of immune targeted therapies

2010
Present

Carcinogenesis

• Initiation
  – Exposure of normal cells to carcinogens produce genetic damage & if not repaired results in irreversible cellular mechanisms

• Promotion
  – Carcinogens or other factors alter the environment & favor growth of mutated cell

• Progression
  – Genetic changes leading to increased cell proliferation & tumor invasion into local tissues or development of metastases
### Genes Involved in Carcinogenesis

#### ONCOGENES

| Genes for growth factors or their receptors | Epidermal growth factor (EGFR) receptor  
| EGFR or Erb-B1 | Human epidermal growth factor receptor 2 (HER-2) |
| HER-2/neu or Erb-B2 | |
| Genes for cytoplasmic relays in stimulatory signaling | Guanine nucleotide-proteins with GTPase activity |
| K-RAS, N-RAS | |
| Genes for transcription factors that activate growth promoting genes | |
| C-MYC, N-MYC | |
| Genes for cytoplasmic Kinases | Non-receptor tyrosine kinase |
| BCR-Abl | |

#### TUMOR SUPPRESSOR GENES

| Genes for proteins in cytoplasm | Adenomatous polyposis coli involved in cell adhesion |
| APC | Codes for a protein that inhibits the stimulatory Ras protein |
| NF-1, NF-2 | |
| Genes for proteins in nucleus | Codes for the pRB protein, a master brake of cell cycle |
| RB1 | Codes for p53 protein, which can halt cell division and induce apoptosis |
| p53 | |
| Genes for protein whose cellular location is unclear | DNA repair, transcriptional regulation |
| BRCA1 | DNA repair |
| BRCA2 | |

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Hallmarks of Cancer

- Unlimited replicative potential
- Tumor promoting inflammation
- Tissue invasion & metastasis
- Promoting angiogenesis
- Mutation potential
- Resisting apoptosis

Escaping growth suppressors
Avoiding immune destruction
Unlimited replicative potential
Tumor promoting inflammation

Types of Cancer Treatments

• Traditional Chemotherapy
• Targeted Therapy
  – Monoclonal Antibodies
  – Small Molecule Inhibitors
• Immunotherapy
  – Cytokine Therapy
  – Checkpoint inhibitors
The Cell Cycle

G2 Phase
Growth & preparation for mitosis

S Phase
DNA Replication

G1 Phase
Growth & normal metabolic roles

M Phase
Cell divides

# Anti-Cancer Cell Cycle Activity

## Cell Cycle Phase Specific Agents

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1 Phase</strong></td>
<td>Asparaginase, Corticosteroids</td>
</tr>
<tr>
<td><strong>M Phase</strong></td>
<td>Vinca alkaloids: Vinblastine, Vincristine, Vinorelbine, Taxanes: Docetaxel, Paclitaxel</td>
</tr>
<tr>
<td><strong>G2 Phase</strong></td>
<td>Bleomycin, Etoposide</td>
</tr>
<tr>
<td><strong>S Phase</strong></td>
<td>Antimetabolites: Azacitadine, Cladribine, Capecitabine, Cytarabine, Decitabine, Fludarabine, Fluorouracil, Gemcitabine, Irinotecan, Hydroxyurea, Methotrexate, Pemetrexed, Topotecan</td>
</tr>
</tbody>
</table>
Anti-Cancer Cell Cycle Activity

<table>
<thead>
<tr>
<th>Cell Cycle Phase Non-Specific Agents</th>
<th>Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating Agents</strong></td>
<td>Melphalan, Busulfan, Chlorambucil, Cyclophosphamide, Ifosfamide, Dacarbazine, Cisplatin, Carboplatin,</td>
</tr>
<tr>
<td><strong>Anthracycline</strong></td>
<td>Doxorubicin, Daunorubicin, Idarubicin</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Nitrosureas, Mitomycin C, Dactinomycin</td>
</tr>
</tbody>
</table>
Chemotherapy Toxicity Profile

- Myelosuppression
  - Thrombocytopenia
  - Anemia
  - Neutropenia
- Mucositis
- Nausea and/or vomiting
- Cutaneous reactions
- Alopecia
- Infertility
- Secondary malignancies
Targeted Therapy

- Drugs that block the growth and spread of cancer by interfering with specific molecules involved in the growth, progression, and spread of cancer
  - Specific therapies that target specific genes or mutations in cancer cells
  - Fewer side effects
Types of Targeted Therapies

Small molecule inhibitors

- (—nib)
- Targets found inside the cell
  - Interfere with cell cycle DNA or RNA synthesis

Monoclonal antibodies

- (—mab)
- Targets found outside the cell
  - Bind to receptors on cell surface
Monoclonal Antibody


Limitations of Targeted Therapy

- Resistance
  - Target itself changes through mutation in which therapy does not interact with
  - Tumor finds a new pathway to achieve tumor growth and does not depend on the target
## Examples of Targeted Therapy

<table>
<thead>
<tr>
<th>PATHWAY</th>
<th>TARGETED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BREAST CANCER</strong></td>
<td></td>
</tr>
<tr>
<td>HER-2</td>
<td>Trastuzumab (Herceptin®), Pertuzumab (Perjeta®), Lapatinib (Tykerb®), Ado-</td>
</tr>
<tr>
<td></td>
<td>trastuzumab emtansine (Kadcyla®)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>mTOR Inhibitor</td>
<td>Everolimus (Afinitor®)</td>
</tr>
<tr>
<td>CDK Inhibitor</td>
<td>Palbociclib (Ibrance®)</td>
</tr>
<tr>
<td><strong>LUNG CANCER</strong></td>
<td></td>
</tr>
<tr>
<td>EGFR Inhibitors</td>
<td>Erlotinib (Tarceva®), Gefitinib (Iressa®), Afatinib (Gilotrif®), Osimertinib</td>
</tr>
<tr>
<td></td>
<td>(Tagrisso®), Necitumumab (Portrazza™)</td>
</tr>
<tr>
<td>ALK Inhibitors</td>
<td>Crizotinib (Xalkori®), Alectinib (Alecensa®), Ceritinib (Zykadia®)</td>
</tr>
<tr>
<td>VEGF Inhibitors</td>
<td>Ramucirumab (Cyramza®), Bevacizumab (Avastin®)</td>
</tr>
<tr>
<td><strong>MELANOMA</strong></td>
<td></td>
</tr>
<tr>
<td>BRAF Inhibitor</td>
<td>Dabrafenib (Tafinlar®), Vemurafenib (Zelboraf®)</td>
</tr>
<tr>
<td>MEK Inhibitor</td>
<td>Trametinib (Mekinist®), Cobimetinib (Cotellic™)</td>
</tr>
</tbody>
</table>
Cellular Signaling Pathways

Human Epithelial Growth Factor Receptor 2 (HER-2) Receptor

• HER-2 is overexpressed
  – 25-30% of breast cancers
  – 20% of gastric cancers

• HER-2 amplification is associated with:
  – Accelerated cell growth
  – Proliferation
  – Poor clinical outcome
The human epidermal growth factor receptor 2 (HER2):HER3 heterodimer.
## HER-2 Receptor Inhibitors Adverse Reactions

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Small Molecule Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trastuzumab</strong> (Herceptin®)</td>
<td>Infusion related Reactions</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>Pulmonary toxicity</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td><strong>Pertuzumab</strong> (Perjeta®)</td>
<td>Infusion related reactions</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td><strong>Ado-trastuzumab emtansine</strong> (Kadcyla®)</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>Infusion related reactions</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary toxicity</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Lapatinib</strong> (Tykerb®)</td>
<td>Cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Toxicity</td>
</tr>
<tr>
<td></td>
<td>QTc Prolongation</td>
</tr>
<tr>
<td></td>
<td>Dermatologic Toxicity</td>
</tr>
</tbody>
</table>
Infusion-Related Reactions

- Fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, hypotension
- Most common with first infusion
- Slow infusion for mild – moderate reactions
- Stop infusion for severe reactions (bronchospasm, hypotension)
Which of the following medications is not expected to be associated with infusion reactions?

1. Trastuzumab
2. Lapatinib
3. Pertuzumab
4. Ado-trastuzumab emtansine
Epidermal Growth Factor Receptor (EGFR)

- Activation of pathway leads to increased cell proliferation, motility, and invasion
- Activation can occur by:
  - Increased expression of EGFR
  - Enhanced ligand production
  - Activating mutations of EGFR within malignant cells.
- EGFR mutations are present in 10-15% of non small cell lung cancers (NSCLC)
## EGFR Inhibitors

<table>
<thead>
<tr>
<th>EGFR Inhibitor</th>
<th>Treatment Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>NSCLC, Pancreatic Cancer</td>
</tr>
<tr>
<td>Gefitinib (Iressa®)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Afatinib (Gilotrif®)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>Colorectal cancer, Head and neck cancer (squamous cell)</td>
</tr>
<tr>
<td>Osimertinib (Tagrisso®)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Necitumumab (Portrazza®)</td>
<td>NSCLC (squamous)</td>
</tr>
<tr>
<td>Panitumumab (Vectibix®)</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Vandetanib (Caprelsa®)</td>
<td>Medullary thyroid cancer</td>
</tr>
</tbody>
</table>
EGFR Inhibitors

Common Adverse Reactions

• Skin toxicity
  – Rash
  – Mucositis
  – Hair changes
  – Paronychia
• Diarrhea
• Pneumonitis
• Ocular toxicity
EGFR Inhibitor Skin Toxicity: Papulopustular (Acneiform) Rash

- Pruritic & tender erythematous papules & pustules develop in skin with high density of sebaceous glands
- Onset: 4-6 weeks after initiation
- Prevention:
  - Moisturizers
  - Sunscreen
  - Avoid alcohol containing skin products

Anaplastic Lymphoma Kinase (ALK)

- Chromosomal inversion leads to fusion of a portion of the ALK gene with the echinoderm microtubule–associated protein-like 4 (EML4) gene resulting in EMLA-4 ALK fusion protein
- EMLA-4 ALK possesses oncologic activity leading to proliferation and survival of cancer cell
- Present in 3-7% of NSCLC
ALK Inhibitors

- Crizotinib (Xalkori®)
- Ceritinib (Zykadia®)
- Alectinib (Alecensa®)

Used in treatment of ALK-positive NSCLC
ALK Inhibitors
Common Adverse Reactions

- Vision changes
- Hypophosphatemia
- Neutropenia
Vascular Endothelial Growth Factor (VEGF) Pathway

• Angiogenesis is the process of creating new blood vessels
  – Increases blood supply to tissue allowing it to grow rapidly

• VEGF binds to tyrosine kinase receptors and results in endothelial cell proliferation, migration, and new vessel formation
# VEGF Inhibitors

<table>
<thead>
<tr>
<th>VEGF Inhibitor</th>
<th>Treatment Indication</th>
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<tbody>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Colorectal cancer, NSCLC, Glioblastoma, renal cell cancer, cervical cancer, ovarian cancer</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza®)</td>
<td>Gastric cancer, NSCLC, colorectal cancer</td>
</tr>
<tr>
<td>Sunitinib (Sutent®)</td>
<td>Gastrointestinal stromal tumor (GIST), Pancreatic neuroendocrine tumors, renal cell cancer</td>
</tr>
<tr>
<td>Sorafenib (Nexavar®)</td>
<td>Hepatocellular cancer, renal cell cancer, thyroid cancer</td>
</tr>
<tr>
<td>Axitinib (Inlyta®)</td>
<td>Renal cell cancer</td>
</tr>
<tr>
<td>Pazopanib (Votrient®)</td>
<td>Renal cell cancer, soft tissue sarcoma, thyroid cancer</td>
</tr>
</tbody>
</table>
VEGF Inhibitor Common Adverse Reactions

- Hypertension
- Proteinuria
- Cardiotoxicity
- Mucositis
- Hand-foot skin reaction
- Delayed wound healing
- Increased risk of internal bleeding
- Perforation of the intestine
MJ is to undergo surgery next month. Which of the following agents should be held at least 4 weeks prior to surgery?

1. Trastuzumab
2. Erlotinib
3. Bevacizumab
4. Crizotinib
Mitogen activated protein kinase (MAPK) Pathway

- Pathway has a critical role in cellular growth & survival
- BRAF mutation rate
  - 50% in melanoma
  - BRAF V600 E most common
  - BRAF V600 mutation leads to hyperactivation of MEK + ERK

# BRAF/MEK Inhibitors

## Common Adverse Reactions

<table>
<thead>
<tr>
<th>BRAF Inhibitors</th>
<th>MEK Inhibitors</th>
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<tbody>
<tr>
<td>Vemurafenib (Zelboraf®)</td>
<td>Cobimetinib (Cotellic®)</td>
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<tr>
<td>Dabrafenib (Tafinlar®)</td>
<td>Trametinib (Mekinist®)</td>
</tr>
</tbody>
</table>

- Skin rash
- Pyrexia
- Arthralgia
- Hyperkeratosis
- Cutaneous squamous cell cancer
- Skin rash
- Fluid retention
- Cardiotoxicity
- Ocular toxicity
Which of the following medications is correctly matched with its mechanism of action?

1. Erlotinib – HER2 receptor inhibitor
2. Dabrafenib – BRAF inhibitor
3. Cobimetinib – MEK inhibitor
4. Crizotinib – EGFR inhibitor
Role of Immunotherapy

• Cancer treatment that enhances your immune system to fight cancer

• Cancer cells can avoid immune surveillance
  – Reducing expression of tumor antigens on their surface
  – Express proteins that induce immune cell inactivation
  – Induce cells in surrounding environment to suppress immune responses
Types of Immunotherapy

• Cytokine Therapy
  – Interleukin-2

• Checkpoint Inhibitors
  – CTLA-4 Inhibitor
    • Ipilimumab
  – PD-1 Inhibitors
    • Nivolumab
    • Pembrolizumab
Cytokine Immunotherapy
High-Dose Interleukin-2 (IL-2)

• Various immunologic effects
  – Promotes the proliferation, differentiation, and recruitment of T and B cells
  – Stimulate synthesis and release of lymphokines
  – Stimulates lymphocyte-mediated cytotoxicity and killer cell activity
High-Dose Interleukin-2 (IL-2) Adverse Reactions

• Cytokine storm
• Affect multiple organ systems
  – Potentially life-threatening
  – Require continuous cardiac monitoring
  – Administer by an experienced oncology team
    • Careful patient screening
    • Diligent adherence to management guidelines
Oncolytic Virus

• Talimogene Laherparepvec (Imlygic®)
  – Genetically modified attenuated herpes simplex virus 1 (HSV) oncolytic virus which selectively replicates in & lyses tumor cells
  – Administered via intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound
Talimogene Laherparepvec (Imlygic<sup>®</sup>)

Adverse Reactions

• Pain or inflammation at injection site
• Myalgia or arthralgia
• Flu-like symptoms
  – Pyrexia, fatigue, chills, headache, dizziness
• Herpes virus infection
Checkpoint Inhibitor
Mechanism of Action

Ipilimumab (Yervoy®)

• Indications and Dosages:
  – Unresectable or metastatic melanoma
    • 3 mg/kg IV every 3 weeks x 4 doses
  – Adjuvant treatment of cutaneous melanoma
    • 10 mg/kg IV every 3 weeks x 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years
Pembrolizumab (Keytruda®)

• Dosage:
  – 2 mg/kg IV every 3 weeks

• Approved Indications:
  – Unresectable or metastatic melanoma
  – Non-small cell lung cancer (NSCLC)
  – Recurrent or metastatic head and neck squamous cell carcinoma
Nivolumab (Opdivo®)

• Dosage:
  – Single Agent: 3 mg/kg IV every 2 weeks
  – In combination with Ipilimumab: 1 mg/kg IV followed by ipilimumab every 3 x 4 doses then single agent 3 mg/kg IV every 2 weeks

• Approved Indications:
  – Metastatic melanoma
  – Renal cell cancer
  – Non-small cell lung cancer (NSCLC)
  – Hodgkin lymphoma
# Immune Related Adverse Events

<table>
<thead>
<tr>
<th>Organ Toxicity</th>
<th>Presentation</th>
<th>Onset of Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, colitis</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Liver</td>
<td>Elevated LFTs</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypophysitis, thyroiditis, adrenal insufficiency</td>
<td>After 9 weeks</td>
</tr>
</tbody>
</table>
Which of the following reactions can occur with immunotherapy?

1. Alopecia
2. Mucositis
3. Papulopustular rash
4. Colitis
# Cancer Treatment Comparison

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Targeted Therapy</th>
<th>Immune Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Cytotoxic</td>
<td>Cytostatic</td>
<td>Enhance anti-tumor immunity</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Rapidly diving cells</td>
<td>Mutated cells</td>
<td>Immune cells</td>
</tr>
<tr>
<td><strong>Mechanism of toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Off target cytotoxicity</td>
<td>Inhibits specific molecular targets and regulates downstream pathways</td>
<td>Loss of immunologic tolerance to self-antigens</td>
</tr>
<tr>
<td></td>
<td>• Drug specific toxicities from metabolism/metabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onset of adverse events</strong></td>
<td>Predictable</td>
<td>Predictable</td>
<td>Unpredictable</td>
</tr>
<tr>
<td><strong>Supportive measures</strong></td>
<td>Targets adverse effect</td>
<td>Targets adverse effect</td>
<td>Targets the immune system</td>
</tr>
</tbody>
</table>

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**Mechanism of Action**
- Chemotherapy: Cytotoxic
- Targeted Therapy: Cytostatic
- Immune Therapy: Enhance anti-tumor immunity

**Target**
- Chemotherapy: Rapidly dividing cells
- Targeted Therapy: Mutated cells
- Immune Therapy: Immune cells

**Mechanism of Toxicity**
- Chemotherapy:
  - Off target cytotoxicity
  - Drug specific toxicities from metabolism/metabolites
- Targeted Therapy: Inhibits specific molecular targets and regulates downstream pathways
- Immune Therapy: Loss of immunologic tolerance to self-antigens

**Onset of Adverse Events**
- Chemotherapy: Predictable
- Targeted Therapy: Predictable
- Immune Therapy: Unpredictable

**Supportive Measures**
- Chemotherapy: Targets adverse effect
- Targeted Therapy: Targets adverse effect
- Immune Therapy: Targets the immune system
Thank You.
References

1. Ipilimumab Prescribing Information. August 2016
2. Nivolumab Prescribing Information. August 2016
4. Ipilimumab Immune-Mediated Adverse Reaction Management Guide