EMERGING IMMUNOTHERAPY

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Objectives

- History
- What is Immunotherapy?
- Types of Immunotherapy
- Current Therapies
- How to Manage
History of Immunotherapy

- William Coley – Father of Immunotherapy
  - Surgeon, Hospital of Ruptured & Crippled
  - Helen Coley Nauts – dtr continued work
- Lloyd J. Old – 1970’s founder modern immunology
- Rapid progression since 1990’s
  - Need for evidence based education
    - Therapies
    - Pathophysiology
    - Toxicities
    - Providing safe and effective care
What Oncology Nurses need to know about Immunotherapy

- Immune System can distinguish between healthy & unhealthy cells
- Engaging the immune system to react to cancer cells as they develop
- Does not directly induce cell death
- Use the immune system actively or passively that results in cancer cell death
- Side effects may be managed differently
- Some require specific targets sites
Types of Immunotherapy

- Check Point Inhibitors
- Chimeric Antigen Receptor (CART-cell)
- Monoclonal Antibodies
- Oncolytic Viral Immunotherapy
Cancer cells cloak themselves to evade bodies immune response and evade body’s protective pathways

Cancer cells are flagged for destruction by activated T-cells which allow immune system to fight malignancies and prevent tissue damage

Boosts immune system to attack at certain point

Solid tumors

Can cause broad inflammatory toxicities
  ▪ Fatigue, colitis, pneumonitis, dermatitis, hepatitis

Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab
- **Types**
  - **Cytotoxic T-lymphocytes – CTLA-4**
    - Ipilimumab – Melanoma
  - **Program cell death - PD-1**
    - Cause increase T-cell formation
    - Pembrolizumab – Melanoma, NSCLC,
    - Nivolumab – RCC, Lung, Colon, Melanoma
  - **Program cell death ligand - PD-L1**
    - Atezolizumab – bladder and NSCLC
    - Durvalumab – urothelial
Human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody

Indication & Administration
- Treatment of unresectable or metastatic melanoma
- Adjuvant treatment of patients with cutaneous melanoma undergone resection
- May be in combination with Nivolumab
- Administer 3mg/kg every 3 weeks over 90 min for 4 cycles
Side Effects & Management

- LFT’s prior to each administration for immune mediated hepatitis
- TSH and evaluate for sign/symptoms endocrinopathy
- Enterocolitis – may need corticosteroids
- Dermatitis – rash and pruitus
  - Discontinue patient with Stevens-Johnson syndrome, toxic epidermal necrolysis or full thickness dermal ulceration
  - Corticosteroids
Pembrolizumab

- Programmed death receptor-1 (PD-1) blocking antibody

Indications & Administration

- Melanoma – unresectable or metastatic
- Non-Small Cell Lung Cancer (NSCLC)
  - Single agent first-line metastatic who’s tumors has PD-L1 expression >50% with no EGFR or ALK genomic tumor aberrations
  - Combination w/ Pemetrexed and Carboplatin, first-line patient with metastatic nonsquamous NSCLC
Indication & Administration cont..

- Recurrent or metastatic head and neck squamous cell cancer after disease progression on or after platinum containing chemotherapy
- Classical Hodgkin Lymphoma - refractory cHL who have relapsed after 3 or more prior lines of therapy
- Urothelial Carcinoma – locally advanced or metastatic not eligible for cisplatin-containing chemotherapy
  - Who have disease progression during or following platinum-containing chemotherapy
Indications & Administration cont..

- Microsatellite Instability-High Cancer
  - Colorectal cancer that has progressed after Fluoropyrimidine, Oxaliplatin and Irinotecan
- Dosing 200mg every 3 weeks
  - Pediatric dosing 2mg/kg

Side Effects & Management – Immune Mediated

- Pneumonitis – withhold for moderate and permanently discontinue for severe or recurrent moderate – may be managed w/ corticosteroids
Side Effects & Management cont..

- Colitis – withhold for moderate and discontinue for severe – may be managed with corticosteroids
- Hepatitis
  - LFT’s
  - Corticosteroids
- Endocrinopathies
  - TSH
  - Monitor for hyperglycemia
  - Corticosteroids, hormone therapy
- Nephritis
Side Effects & Management cont..

- Nephritis and Renal Dysfunction
  - Monitor for changes renal function
  - Corticosteroids
Nivolumab

- **Indication & Administration**
  - BRAF V600 wild-type unresectable or metastatic melanoma
  - BRAF V600 mutation-positive unresectable or metastatic melanoma
  - Unresectable or metastatic melanoma in combination with Ipilimumab.
  - Metastatic non-small cell lung cancer after progression on platinum-based chemotherapy.
  - Advanced renal cell carcinoma who have received prior anti-angiogenic therapy
Indication & Administration cont..

- Classical Hodgkin lymphoma after
  - Autologous hematopoietic stem cell transplantation and Brentuximab
  - 3 or more lines of systemic therapy that includes autologous HSCT
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-based therapy
- Locally advanced or metastatic urothelial carcinoma
  - Have disease progression during or following platinum-containing chemotherapy
  - Disease progression within 12 months neo/adjuvant treatment with platinum-containing chemotherapy
Nivolumab cont..

- Indication & Administration cont..
  - Opdivo 240mg every 2 weeks
    - Melanoma, NSCLC, renal cell, urothelial
  - Opdivo 1mg/kg followed by Ipilimumab every 3 weeks for 4 cycles then Opdivo 240mg every 2 weeks
    - Melanoma
  - Opdivo 3mg/kg every 2 weeks
    - Classical Hodgkin lymphoma, head and neck
Side Effects & Management – Immune Mediated

- Pneumonitis
- Colitis
- Hepatitis
- Endocrinopathies
- Renal dysfunction
- Dermatitis
- Encephalitis
- **Indication & Administration**
  - Locally advanced or metastatic urothelial carcinoma
    - Not eligible for cisplatin-containing chemotherapy
    - Have disease progression during or following platinum-containing chemotherapy, or within 12 months of neo/adjuvant chemotherapy
  - Metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy.
- **Tecentriq 1200mg every 3 weeks**
Atezolizumab

- Side Effects & Management – Immune Mediated
  - Pneumonitis
  - Hepatitis
  - Colitis
  - Endocrinopathies
  - Myasthenic Syndrome/Myasthenia Gravis
  - Ocular Inflammatory Toxicity
  - Pancreatitis
Indication & Administration

- Locally advanced or metastatic urothelial carcinoma
  - Disease progression during or following platinum-containing chemotherapy
  - Disease progression within 12 months of neo/adjuvant treatment with platinum-containing chemotherapy
- Imfinzi 10mg/kg every 2 weeks

Side Effects & Management – Immune Mediated

- Pneumonitis
- Hepatitis
Durvalumab cont..

- Side Effects & Management – Immune Mediated cont..
  - Colitis
  - Edocrinopathies
  - Nephritis
  - Infection
Chimeric Antigen Receptor (CAR) T-cell

- An artificially T-cell receptor, genetically engineered to target specific tumor antigen or tumor marker
  - Currently clinical trials
    - Leukemias
    - Lymphomas
    - Myeloma
  - CART 19 phase I & II trials
- Work extracellular and intracellular
- Manufactured T-cells from person and then given back
- Goal is for T-cells to live for months to years and continue to be effective.
Chimeric Antigen Receptor CAR) T-cell

- Toxicity
  - Cytokine release syndrome
    - Fever, myalgia, HA in mild to moderate cases
    - Hypotension, capillary leaks
  - Neurotoxicity
    - CNS depression
    - Swelling
Monoclonal Antibodies

- Work on specific antigen receptors and act as natural antibodies
- Can be combined w/ radiation
- Cytokine and tumor invasion
- Acute infusion reactions/cytokine release reaction
- Rituximab, Trastuzumab, Denosumab, Cetuximab, Daratumumab, Olaratumab, Bevacizumab, Ramucirumab
<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug</th>
<th>Side Effect</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno of stomach or GE</td>
<td>Ramucirumab (Cyramza)</td>
<td>Hypertension, neutropenia, fatigue, stomatitis</td>
<td>Human MA</td>
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<td>junction</td>
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<tr>
<td>Bone metastatasis</td>
<td>Denosumab (Xgeva)</td>
<td>Hpocalcemia, osteonecrosis</td>
<td>Humanized MA</td>
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<tr>
<td>Breast</td>
<td>Trastuzumab (Herceptin), Ado-trastuzumab</td>
<td>Cardio-toxicity, diarrhea, fatigue, arterial/venous</td>
<td>Humanized MA</td>
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<tr>
<td></td>
<td>emtansine (Kadcyla)</td>
<td>thromboembolus, hypertension, PML</td>
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<td>Pertuzumab (Perjeta)</td>
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<tr>
<td>Cervical, Ovarian</td>
<td>Bevacizumab (Avastin)</td>
<td>Hypertension, PML, cardio-toxicity, pulmonary toxicity</td>
<td>Humanized MA</td>
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## Monoclonal Antibodies

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<tr>
<td>Colorectal</td>
<td>Bevacizumab, Cetuximab (Erbitux), Panitumumab (Vectibix), Ramucirumab (Cyramza)</td>
<td>Cardio-toxicity, pulmonary toxicity, arterial/venous thromboembolus, hypertension, PML, rash</td>
<td>Human, humanized and chimeric MA</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Bevacizumab (Avastin)</td>
<td>Hypertension, PML, cardio-toxicity, pulmonary toxicity</td>
<td>Humanized MA</td>
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<tr>
<td>Head and neck</td>
<td>Cetuximab (Erbitux)</td>
<td>Cardio-toxicity, pulmonary toxicity, arterial/venous thromboembolus, hypertension, PML, rash,</td>
<td>Chimeric MA</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (Opdivo), Pembrolizumab (Keytruda)</td>
<td>Immune-mediated - Endocrinopathies, pneumonitis, colitis, hepatitis,</td>
<td>Human and humanized MA</td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td>Bevacizumab (Avastin), Nivolumab (Opdivo)</td>
<td>Hypertension, arterial/venous thromboembolus, Immune-mediated</td>
<td>Human and humanized MA</td>
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<tr>
<td>Leukemia</td>
<td>Rituximab (Rituxan), Blinatumomab (Blincyto), Alemtuzumab (Campath), Obinutuzumab (Gazyva), Ofatumumab (Arzerra), Gemtuzumab (Mylotarg)</td>
<td>CRS, TLS, neurotoxicities, mucositis, hepatitis B reactivation, immunosuppression, fatigue, nausea, diarrhea, shortness of breath, dermatitis, peripheral edema</td>
<td>Human, humanized, murine, and chimeric MA</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Ipilimumab (Yervoy), Nivolumab (Opdiov), Pembrolizumab (Keytruda)</td>
<td>Immune-mediated</td>
<td>Human and humanized MA</td>
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<tr>
<td>Multiple Myeloma</td>
<td>Daratumumab (Darzalex), Elotuzumab (Empliciti)</td>
<td>CRS, TLS, neurotoxicities, mucositis, hepatitis B reactivation, immuno-suppression, fatigue, nausea, diarrhea, neutropenia, dermatitis, peripheral edema</td>
<td>Human and humanized MA</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Dinutuximab (Unituxin)</td>
<td>Capillary leak syndrome, sepsis, hypotension, thrombocytopenia</td>
<td>Chimeric MA</td>
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<td>Non-small Cell Lung cancer</td>
<td>Bevacizumab (Avastin), Nivolumab (Opdivo), Prembolizumab (Keytruda), Atezolizumab (Tecentriq), Ramucirumab (Cyramza), Necitumumab (Portrazza)</td>
<td>Cardio-toxicity, pu. Toxicity, thromboembolus, hypertension, PML, Immune-mediated, rash, diarrhea, fatigue</td>
<td>Human and humanized MA</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Olaratumab (Lartruvo)</td>
<td>Nausea, vomiting, fatigue, pain, mucositis</td>
<td>Human MA</td>
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<tr>
<td>Urothelial</td>
<td>Atezolizumab (Tecentriq),</td>
<td>Immune-mediated, rash, neutropenia</td>
<td>Humanized MA</td>
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<tr>
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<td>Durvalumab (Imfinzi)</td>
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Oncolytic Viral Immunotherapy

- Live virus produce tumor-toxic cytokines or antitumor host response
- 4 mechanisms of actions
  - Viral receptor response
  - Cytokine release
  - Nucleus replication
  - Extracellular immune response
- Safety issues with administration and disposal
- Patient/caregiver education - cross contamination, avoidance of contact with immunocompromised
- Metastatic Melanoma
  - Talimogene – injected directly into tumor/lesion
Nursing Implications

- Focused assessment
  - Lab
    - TSH
    - Pituitary Function
    - LFT’s
    - Pancreatic enzymes
  - Physical
    - Weight, fatigue, pain, diarrhea
  - Psychiatric
    - Mood changes
    - Alteration in sleep – hyper/hypothyroidism
Education

- Standards
  - Hand hygiene
  - Infection control
  - Hydration
  - Safe sexual practices
  - GI education
Immunotherapy is not new, it is ever changing and evolving.

New challenges in the management of patients

Stress of keeping up with changes
Questions?