Cancer is not a new issue

- First known case of cancer
- Ancient Egyptian papyrus included description of 8 cases of tumor or ulcers
Cancer is common

- Lifetime probability of cancer (any site) is 1 in 3
- Cancer remains the second leading cause of death
- Treatment is improving cancer survival but toxicity is a persistent issue

Estimated New Cancer Cases* in the US in 2019

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>870,970</td>
<td>891,480</td>
</tr>
</tbody>
</table>

- Prostate: 20%
- Lung & bronchus: 13%
- Colon & rectum: 9%
- Urinary bladder: 7%
- Melanoma of skin: 7%
- Kidney & renal pelvis: 5%
- Non-Hodgkin lymphoma: 5%
- Oral cavity & pharynx: 4%
- Leukemia: 4%
- Pancreas: 3%
- All other sites: 22%

*Includes males and females with site-specific cancers and other cancers except cutaneous.


The Early Days of Chemotherapy

Nitrogen Mustard: From weapon of destruction in World War I to weapon against cancer

Blood and bone marrow in mustard gas poisoning

Sidney Farber: The Father of Modern Chemotherapy

(CC BY 4.0) Auckland Museum
Characteristics of cancer cell

- Produces its own growth factors
- Not inhibited by growth factor inhibitors
- Evade apoptosis (programmed cell death)
- Can divide infinitely
- Can produced its own blood vessels (angiogenesis)
- Can invade tissue and metastasize
- Can evade the immune system
Treating Cancer is Complex

Unique characteristics of a cancer cell

- Produces its own growth factors
- Not inhibited by growth factor inhibitors
- Evade apoptosis (programmed cell death)
- Can divide infinitely
- Can produce its own blood vessels (angiogenesis)
- Can invade tissue and metastasize
- Can evade the immune system

Cancer cells are abnormal in multiple ways
- Treatment aims to exploit these growth pathways as weaknesses
- We will review:
  - Cytotoxic Chemotherapy
  - Targeted Therapy
  - Immunotherapy

Cancer Therapy is Evolving

Cytotoxic chemotherapy
- Anthracyclines
- Alkylating agents
- Anti-metabolites
- Mitotic inhibitors

Targeted Therapy
- Monoclonal Antibodies
- Tyrosine kinase inhibitors
- Hormonal therapies

Immunotherapy
- Checkpoint inhibitors: CTLA4 and PD/PDL1

Hybrid Therapies: Chemo-Immunotherapy
Chemotherapy: Mechanism of action

- Chemotherapy = cytotoxic medications

  - Alkylating Agents
  - Platinum agents
  - Anti-metabolites
  - Nucleoside analogs
  - Topoisomerase inhibitors
  - Anti-Microtubule agents

![Cell Cycle Diagram](https://creativecommons.org/licenses/by-sa/3.0)

Chemotherapy Toxicities

<table>
<thead>
<tr>
<th>Common Side Effects</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or vomiting</td>
<td>Anti-emetics</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Cryotherapy, mouth rinses</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Anti-motility agents</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Cryotherapy</td>
</tr>
<tr>
<td>Cytopenias, including anemia and neutropenia</td>
<td>Prophylactic G-CSF (neupogen/neulasta), transfusion support</td>
</tr>
</tbody>
</table>
### Specific Toxicities - Acute

- **Busulfan and Bleomycin**
  - Pulmonary fibrosis/pneumonitis
- **Cisplatin**
  - Ototoxicity
  - Nephrotoxicity
- **5-Fluorouracil (5-FU)**
  - Hand-foot syndrome
- **Oxaliplatin and Paclitaxel**
  - Sensory neuropathy
- **Vincristine/vinblastine**
  - Sensory-motor neuropathy
- **Irinotecan**
  - Diarrhea

### Chronic Toxicities of Chemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Drugs (examples)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>Doxorubicin</td>
<td>Lifetime limit on drug exposure</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Daunorubicin</td>
<td>Monitoring on treatment</td>
</tr>
<tr>
<td>Sensory Neuropathy</td>
<td>Taxanes</td>
<td>Gabapentin</td>
</tr>
<tr>
<td></td>
<td>Platinum drugs</td>
<td>Lyrica</td>
</tr>
<tr>
<td>Infertility</td>
<td>Alkylators</td>
<td>Sperm banking or Egg harvest</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Hormonal agents</td>
<td></td>
</tr>
<tr>
<td>Secondary Malignancies – MDS</td>
<td>Alkylators (5-7 years)</td>
<td>Monitor blood counts</td>
</tr>
<tr>
<td>and leukemia</td>
<td>Topoisomerase inhibitors (1-3 years)</td>
<td></td>
</tr>
<tr>
<td>Secondary Malignancies</td>
<td>Multiple agents and radiation</td>
<td>Cancer screening</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>Multiple agents and radiation</td>
<td>Exercise, healthy weight</td>
</tr>
</tbody>
</table>
Managing Complications of Chemotherapy

Edmund Folefac, MBCHB
Assistant Professor – Clinical
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

Targeted Therapy

To understand how these therapies work, we must first understand:

1) how the normal cell operates
   and
2) what makes cancer cells different
Chemotherapy vs targeted therapy

Ideal Characteristics of a Targeted Therapy

- Target should be essential to the malignant cell survival
- Target is not expressed on normal cells
- Target inhibition leads to malignant cell death with minimal effect on normal cell function
- Target can be reliably identified with available testing
- Inhibition of target should correlate with clinical benefit
**Current Targeted Therapies**

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Mechanism of Action</th>
<th>Examples</th>
<th>Cancer Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal therapy</td>
<td>Estrogen blockade</td>
<td>• Tamoxifen, aromatase inhibitors, Leuprolide, bicalutamide</td>
<td>Breast Cancer, Prostate Cancer</td>
</tr>
<tr>
<td></td>
<td>Testosterone blockade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosine Kinase Inhibitors</td>
<td>Small molecule blocks cell signaling pathway</td>
<td>• Dabrafenib (BRAF), Erlotinib (EGFR), Pazopanib (VEGF), Palbociclib (PARP inhibitor)</td>
<td>Melanoma, Lung cancer, Kidney cancer, Breast cancer</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Antibody binding to block cell signaling pathway</td>
<td>• Cetuximab (EGFR), Bevacizumab (VEGF), Trastuzumab (HER2)</td>
<td>Head and neck cancer, Lung cancer, Breast cancer</td>
</tr>
</tbody>
</table>
Other skin changes

- Rash (acneiform,)
- Nail changes,
- hand-foot syndrome,
- Hyperpigmentation
- Dry skin
- Telangiectasia

Targeted Therapy Skin Toxicity

- Common with multiple targeted agents especially EGFR– TKI and mAB
- Tends to be dose dependent
- Signs and Symptoms:
  - Pruritis
  - Diffuse rash – commonly on face/chest/back
  - Often occurs in seborrheic areas
  - May be worsened by sun exposure
- Associated with increased risk of Staph super-infection
Skin Toxicity: Prevention and Treatment

- Keep skin moist
- Avoid sun exposure or use sunscreen
- Apply emollient generously
- Topical steroids may be useful
- Topical Antibiotics: Clindamycin, metronidazole
- Oral minocycline, tetracycline and doxycycline may be necessary in some cases
- Antihistamines for itching not responsive to topical steroids

GI Toxicities

- Diarrhea – very common with targeted therapy
  - ✔ EGFR inhibitors in particular
- Intestinal bleeding and perforations
  - ✔ Primarily with VEGF inhibitors
- Hepatotoxicity
  - ✔ Common with ALK inhibitors
- Elevated pancreatic enzymes
Diarrhea Management

- First - Exclude other causes!
- Loperamide
- Octreotide (SC)
- Hold drug or dose reduction by oncology
- Severe diarrhea
  - Hospitalization
  - Replace electrolytes

Cardiovascular Toxicities

- Hypertension is one of the most common cardiac toxicities
  - Commonly associated with VEGF inhibitors
- HTN management: ACE-inhibitors are a preferred agent
- Dose reduction or holding drug may also be required
- Avoid these drugs in patients with uncontrollable HTN
- QT prolongation is another potential toxicity
- Thromboembolic disease and Bleeding are also possible
Cardiac Toxicity of Targeted Therapy

- Cardiomyopathy
  - Type I: Kills cardiac cells but have minimal effects
  - Type II: Prevents coordinated contraction of cardiac myofibrils but do not kill cardiac cells
- Cardiotoxic drugs require heart function monitoring

Cardiac Toxicity of Targeted Therapy

- Cardiac myocytes express Human epidermal growth factors
  - Trastuzumab (anti-HER2 mAb) induces mitochondria apoptosis, thus affect cardiac contractility
  - Osimertinib (anti-EGFR TKI) may also cause cardiomyopathy
- Trastuzumab induced cardiotoxicity recovery ranges from months to > 1 year
Renal Toxicity

- Multiple Renal Toxicities may be seen, particularly with VEGF inhibitors
- Glomerulonephritis: VEGF is expressed on nephrons – VEGF inhibitors are associated with proteinuria
- Minimal change, membranoproliferative and cryoglobulinemic /focal segmental nephritis
- Tubular acidosis, interstitial nephritis, Distal tubular dysfunction, Microangiopathy renal thrombosis
- Interstitial nephritis- allergic nephritis (fever, rash, proteinuria, eosinophilia and eosinophiluria)
- Acute tubular necrosis, crystal nephropathy, tubular atrophy, interstitial fibrosis

Examples of some targeted therapies and their renal toxicities

<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>Tyrosine kinase inhibitors</th>
<th>mTOR inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Sunitinib</td>
<td>Proteinuria</td>
</tr>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Acute renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>Vatalanib</td>
<td>Focal glomerulosclerosis</td>
</tr>
<tr>
<td></td>
<td>Vandetanib</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td></td>
<td>Axitinib</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td></td>
</tr>
</tbody>
</table>

- Proteinuria
- Nephrotic syndrome
- Glomerulonephritis
- Interstitial nephritis
- Thrombotic microangiopathy
- Hypomagnesaemia
- Interstitial nephritis
- Proteinuria
- Proteinuria
- Proteinuria
- Proteinuria
- Proteinuria
- Proteinuria
- Focal glomerulosclerosis
- Acute tubular necrosis
- Thrombotic microangiopathy
delete?

Bertino, Erin, 2/26/2019
FDA timeline for immunotherapy approval

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>FDA approval for sipuleucel-T targeting a specific cancer antigen was the first FDA-approved specific immunotherapy.</td>
</tr>
<tr>
<td>2012</td>
<td>Pembrolizumab approved for metastatic melanoma.</td>
</tr>
<tr>
<td>2013</td>
<td>Nivolumab approved for metastatic melanoma.</td>
</tr>
<tr>
<td>2014</td>
<td>Atezolizumab approved for non-small cell lung cancer.</td>
</tr>
<tr>
<td>2015</td>
<td>Ipilimumab approved for metastatic melanoma.</td>
</tr>
<tr>
<td>2016</td>
<td>Pembrolizumab approved for PD-L1+ NSCLC.</td>
</tr>
<tr>
<td>2017</td>
<td>Nivolumab approved for NSCLC.</td>
</tr>
</tbody>
</table>

Immunotherapy Mechanism of Action

Nobel Prize for Medicine 2018
Cancer Therapy by Inhibition of Negative Immune Regulation (CTLA4, PD1)

Author - Guido4
(CC BY-SA 3.0) - https://creativecommons.org/licenses/by-sa/3.0/deed.en
Managing Complications of Chemotherapy

Erin Bertino, MD
Associate Professor of Internal Medicine
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

Current Immunotherapy Agents

• PD-1/PD-L1 Inhibitors
  ✓ Pembrolizumab
  ✓ Atezolizumab
  ✓ Durvalumab
  ✓ Avelumab
  ✓ Cemiplimab
  ✓ Nivolumab
• CTLA-4 Inhibitors
  ✓ Ipilimumab
Immunotherapy Toxicity Overview

- Autoimmune toxicity may affect any organ system
- May mimic other conditions
- May be acute or delayed
- Common Toxicities (≥ 10%)
  ✓ Fatigue
  ✓ Rash/pruritis
  ✓ Diarrhea
- Uncommon Toxicities (< 10%)
  ✓ Hepatitis
  ✓ Pneumonitis
  ✓ Endocrinopathies
  ✓ Cardiac
  ✓ Pancreatitis

Timing is Variable

Immunotherapy Toxicities – General Management

Grade 1 - Mild symptoms
- Supportive measures, Continue immune therapy

Grade 2 - Moderate symptoms
- Supportive measures, Hold immune therapy
- May add steroids*

Grade 3-4 - Severe symptoms
- Discontinue/Delay Immune therapy
- Add steroids* or increase steroid dose

GI Toxicity

- Colitis is one of the most common toxicities
  - Any grade – 30%, severe cases <10%
  - Rule out infection, including C diff infection
  - Consider Colonoscopy for severe cases
- Hepatitis
  - Increased risk with combination therapy
  - Rule out infection, metastatic disease, steatohepatitis
- Pancreatitis
  - Amylase, lipase elevation
  - May be associated with hyperglycemia/diabetes

Author - BruceBlaus (CC BY 3.0) - https://creativecommons.org/licenses/by/3.0/deed.en
Endocrine Toxicity

- Thyroid dysfunction (>10%)
  - Replacement therapy for hypothyroidism
  - Symptom control for hyperthyroidism
- Hypophysitis (<5%)
  - Non-specific symptoms: headache, fatigue
  - Cortisol, ACTH, thyroid function testing
- Adrenal insufficiency (rare)
  - Dehydration, hypotension, hyperkalemia, hyponatremia
  - Steroid replacement
- Diabetes (rare)
  - Anti-GAD or anti-islet antibodies may be present
  - Insulin therapy may be required

Pulmonary Toxicity - Pneumonitis

- Focal or diffuse inflammation of lung parenchyma
- Onset may be early or late
- Differential includes infection, COPD exacerbation, and disease progression
- Bronchoscopy may be helpful if patient is stable
- Empiric therapy: Steroids and antibiotics
Immunotherapy Skin Toxicity

- **Rash/Inflammatory Dermatitis**
  - Variable: erythema, maculopapular rash, eczematous/ psoriasiform
  - *Differential:* drug rash, infection (cellulitis), autoimmune conditions, hand-foot syndrome

- **Bullous Dermatoses (rare)**
  - Bullae/blisters, sloughing possible
  - *Differential:* drug reaction, bullous pemphigoid, infection (esp. viral), friction/trauma

- **Stevens Johnson Syndrome (SJS), toxic epidermal necrosis (TEN),**
  - Severe alteration to skin structure or function; mucous membrane involvement
  - *Differential:* drug reactions including paraneoplastic pemphigus, autoimmune blistering dermatoses

- **Management:** Moisturize, topical steroids, systemic steroids if severe
Rare Toxicities

- Cardiac
  - May mimic heart failure or acute MI
  - Cardiac MRI may be helpful
  - High dose steroids may help
- Neurologic
  - Range of presentations including encephalitis, Guillan-Barre, or transverse myelitis
- Ocular – Uveitis
- Rheumatologic
  - Inflammatory Arthritis
  - Myositis
  - Sicca syndrome
- Renal
  - Kidney failure may be seen

Managing Complications of Oncology Treatment - Summary

- Cancer treatment is evolving
- Chemotherapy
  - May be used alone or in combination with other treatments
  - Common side effects include hair loss, fatigue, nausea, mucositis, cytopenias
- Targeted Therapy
  - Side effects vary depending on drug target
  - Supportive care is helpful, oncology may also need to hold/adjust drug
- Immunotherapy
  - Toxicities may affect any organ and may mimic other conditions
  - Immunosuppression is the backbone of treatment of toxicity