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

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>Cancer Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>22%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Kidney &amp; ureter</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Estimated by Amer Cancer Society

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
### Timeline: Development of cancer therapeutics

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Single agent chemotherapy</td>
<td>Combination chemotherapy</td>
<td>Combination chemotherapy emerges</td>
<td>Intro of oral chemotherapy treatments</td>
<td>New era of molecular biology including biologics</td>
<td>First immunotherapy drug approved to 24+ biomarkers</td>
</tr>
</tbody>
</table>

### Characteristics of 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

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### 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**
- **Targeted Therapy**
- **Immunotherapy**
- **Monoclonal Antibodies**
- **Tyrosine kinase inhibitors**
- **Hormonal therapies**
- **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

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, Daunorubicin</td>
<td>Lifetime limit on drug exposure</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>Monitoring on treatment</td>
</tr>
<tr>
<td>Sensory Neuropathy</td>
<td>Taxanes, Platinum drugs</td>
<td>Gabapentin, Lyncya</td>
</tr>
<tr>
<td>Infertility</td>
<td>Alkylators, Hormonal agents</td>
<td>Sperm banking or Egg harvest</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Malignancies</td>
<td>Alkylators (5-7 years), Topoisomerase inhibitors (1-3 years)</td>
<td>Monitor blood counts, 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

Targeted Therapies Pick Out Cancer Cells

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,</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td></td>
<td>Testosterone blockade</td>
<td>bicalutamide</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>Tyrosine Kinase</td>
<td>Small molecule</td>
<td>Dabrafenib (BRAF), Erlotinib (EGFR), Pazopanib</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>blocks cell signaling pathway</td>
<td>(VEGF), Palbociclib (PARP inhibitor)</td>
<td>Lung cancer, Kidney cancer, Breast cancer</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Antibody binding to cell signaling pathway</td>
<td>Cetuximab (EGFR), Bevacizumab (VEGF), Trastuzumab</td>
<td>Head and neck cancer, Lung cancer, Breast cancer</td>
</tr>
</tbody>
</table>

### Targeted Therapy Toxicity

Toxicity may be “on target” or “off target”

- **“On target” toxicity**: effect of the drug on a target that is expressed by both the cancer and normal tissue cell
- **“Off target” toxicity**: result when a drug affects the target essential for normal tissue cells but not essential for cancer cell survival – “bystander effect”

Toxicity also depends on drug target:
- Skin (rash)
- Gastrointestinal/Liver (diarrhea, hepatitis)
- Cardiac (cardiomyopathy, QT changes)
- Renal
- Others may also occur – ocular, endocrine, etc

### Targeted Therapy Skin Toxicity

**Acneiform**

- 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

### Other skin changes

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

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>Proteinuria</th>
<th>Nephrotic syndrome</th>
<th>Glomerulonephritis</th>
<th>Interstitial nephritis</th>
<th>Thrombotic microangiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
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<tr>
<td>Cetuximab</td>
<td></td>
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<tr>
<td>Panitumumab</td>
<td></td>
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<table>
<thead>
<tr>
<th>Tyrosine kinase inhibitors</th>
<th>Proteinuria</th>
<th>Interstitial nephritis</th>
<th>Thrombotic microangiopathy</th>
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</thead>
<tbody>
<tr>
<td>Bunitinib</td>
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<tr>
<td>Sorafenib</td>
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<td></td>
<td></td>
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<tr>
<td>Vatalanib</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Axitinib</td>
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<tr>
<th>mTOR inhibitors</th>
<th>Proteinuria</th>
<th>Acute renal dysfunction</th>
<th>Focal glomerulosclerosis</th>
<th>Acute tubular necrosis</th>
<th>Thrombotic microangiopathy</th>
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Bertino, Erin, 2/26/2019
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Erin Bertino, MD
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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

Immunotherapy Toxicities – General Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Supportive measures, Continue immune therapy</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Supportive measures, Hold immune therapy, Add steroids* if needed</td>
</tr>
<tr>
<td>3-4</td>
<td>Severe</td>
<td>Discontinue/Delay immune therapy, Add steroids* or increase steroid dose</td>
</tr>
</tbody>
</table>

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 hyperglicemia/diabetes

GI Toxicity Time is Variable

**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

**Immunotherapy Skin Toxicity**

- 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