Managing Complications of Chemotherapy

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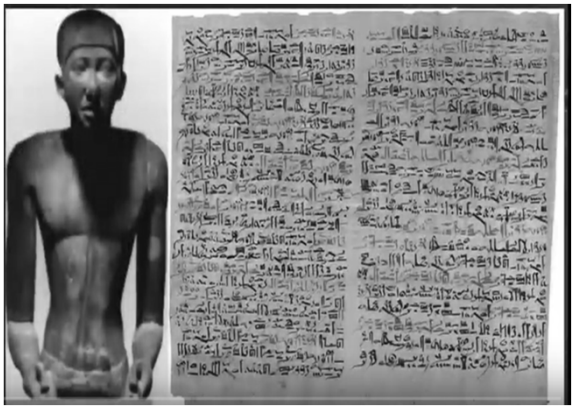
Cancer is not a new issue

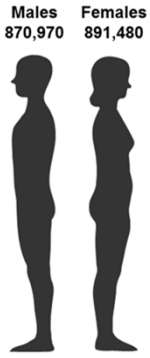


- First known case of cancer
- Ancient Egyptian papyrus included description of 8 cases of tumor or ulcers

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



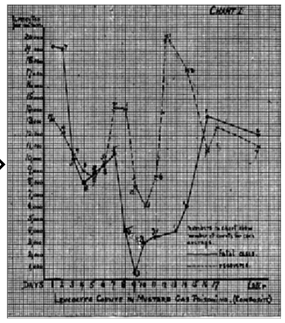
Males		Females	
Prostate	20%	30%	Breast
Lung & bronchus	13%	13%	Lung & bronchus
Colon & rectum	9%	7%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	7%	5%	Melanoma of skin
Kidney & renal pelvis	5%	4%	Thyroid
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Oral cavity & pharynx	4%	3%	Kidney & renal pelvis
Leukemia	4%	3%	Pancreas
Pancreas	3%	3%	Leukemia
All other sites	22%	21%	All other sites

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

***Cancer Facts & Figures 2019*. Published online January 8, 2019. American Cancer Society, Atlanta, Ga.**

The Early Days of Chemotherapy

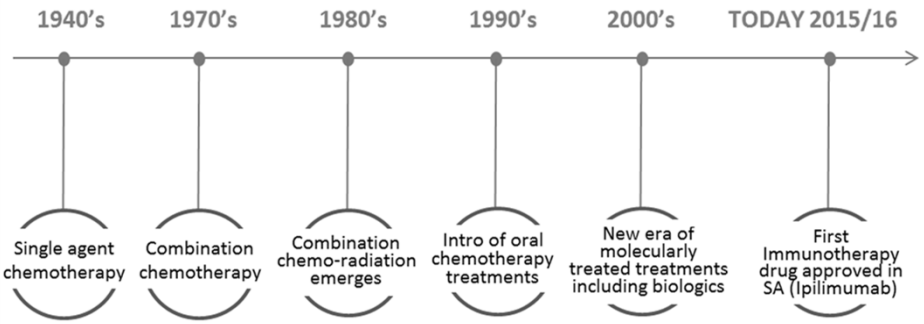
Nitrogen Mustard: From weapon of destruction in World War I to weapon against cancer



Blood and bone marrow in mustard gas poisoning By E.B. and Helen Krumbhaar J Med Res. 1919 Sep; 40(3): 497–508.3.

Sidney Farber: The Father of Modern Chemotherapy

Timeline: Development of cancer therapeutics



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**

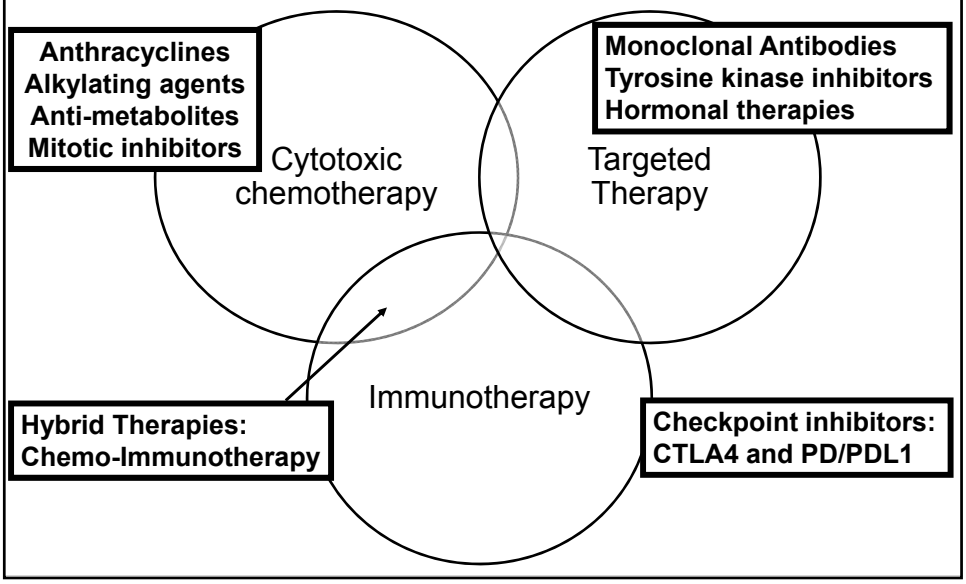
Treating Cancer is Complex

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

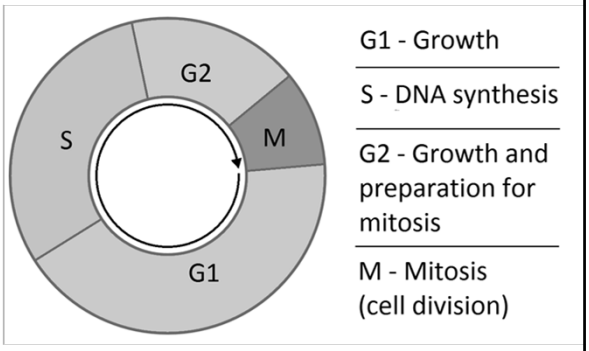
Cancer Therapy is Evolving



Chemotherapy: Mechanism of action

- **Chemotherapy = cytotoxic medications**

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



Chemotherapy Toxicities

Common Side Effects	**Management**
Nausea and/or vomiting	Anti-emetics
Mucositis	Cryotherapy, mouth rinses
Diarrhea	Anti-motility agents
Alopecia	Cryotherapy
Cytopenias, including anemia and neutropenia	Prophylactic G-CSF (neupogen/neulasta), transfusion support

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

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

Managing Complications of Chemotherapy

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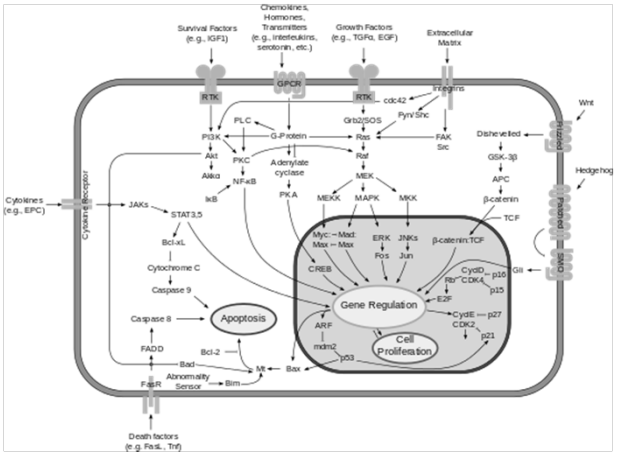
Targeted Therapy

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

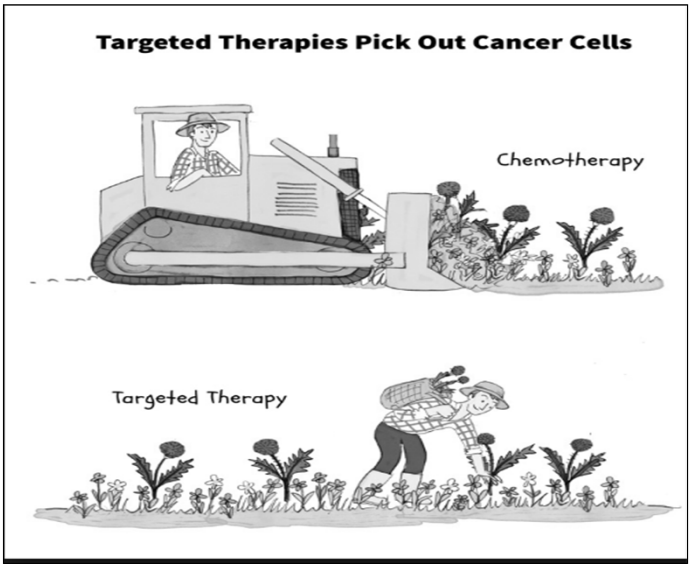
1) how the normal cell operates

<u>and</u>

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

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

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 results 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**

Other skin changes

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

Targeted Therapy Skin Toxicity

Acneiform

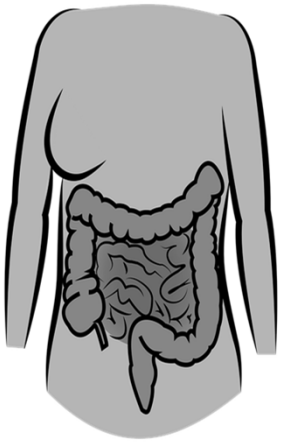
- Common with multiple targeted agents especially EGFR– TKI and mAB
- Tends to be dose dependent
- Signs and Symptoms:
  - Pruritis
  - Diffuse rash – commonly on face/chest/back
  - Often occurs in seborrheic areas
  - May be worsened by sun exposure
- Associated with increased risk of Staph super-infection

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

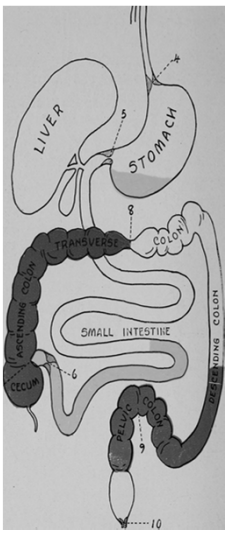
GI Toxicities

- 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



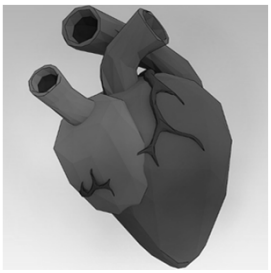
Diarrhea Management

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



Cardiovascular Toxicities

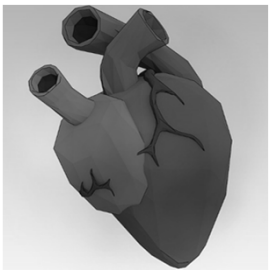
- Hypertension is one of the most common cardiac toxicities
  - ✓ Commonly associated with VEGF inhibitors
- HTN management: ACE-inhibitors are a preferred agent
- Dose reduction or holding drug may also be required
- Avoid these drugs in patients with uncontrollable HTN



- QT prolongation is another potential toxicity
- Thromboembolic disease and Bleeding are also possible

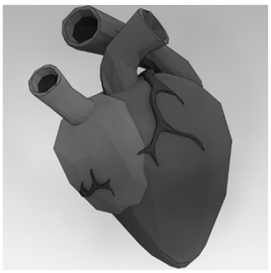
Cardiac Toxicity of Targeted Therapy

- 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

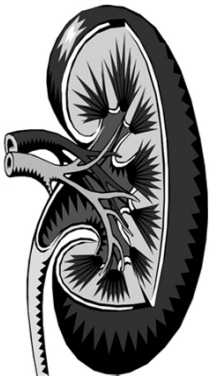


Cardiac Toxicity of Targeted Therapy

- 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

Monoclonal antibodies	
Bevacizumab	Proteinuria Nephrotic syndrome Glomerulonephritis Interstitial nephritis Thrombotic microangiopathy
Cetuximab	Hypomagnesaemia
Panitunimab	Hypomagnesaemia
Tyrosine kinase inhibitors	
Sunitinib	Interstitial nephritis Thrombotic microangiopathy
Sorafenib	Interstitial nephritis
Vatalanib	Proteinuria
Vandetanib	Proteinuria
Axitinib	Proteinuria
Imatinib	Fanconi Syndrome
mTOR inhibitors	Proteinuria Acute renal dysfunction Focal glomerulosclerosis Acute tubular necrosis Thrombotic microangiopathy

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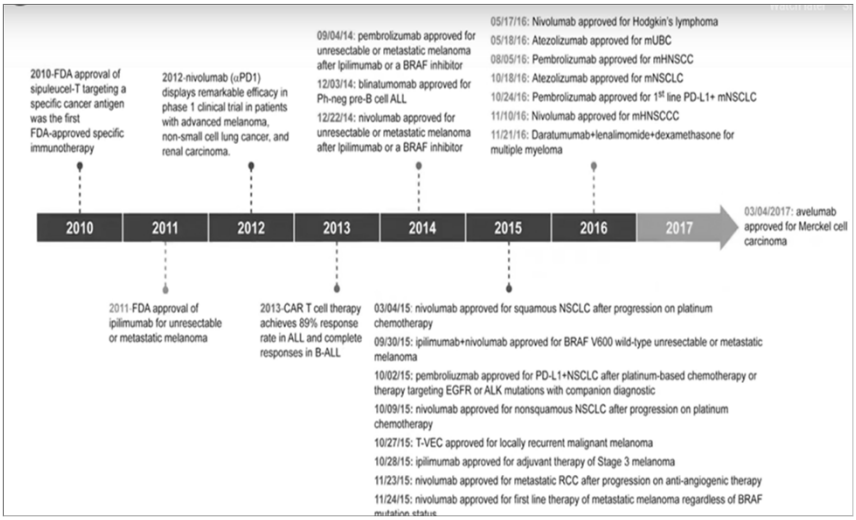
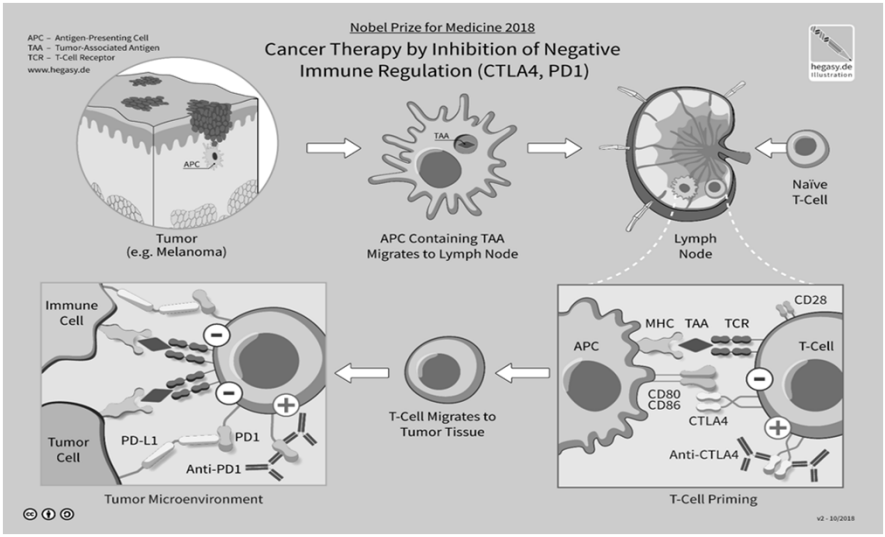
Bertino, Erin, 2/26/2019

FDA timeline for immunotherapy approval



Immunotherapy Mechanism of Action



Managing Complications of Chemotherapy

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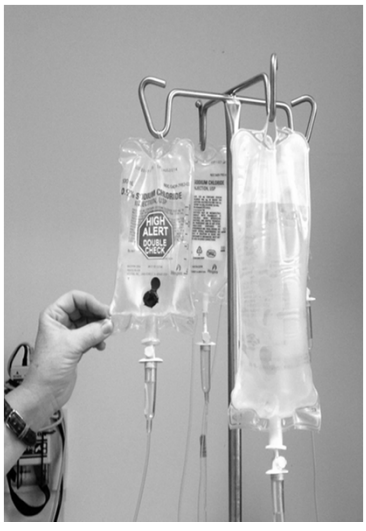
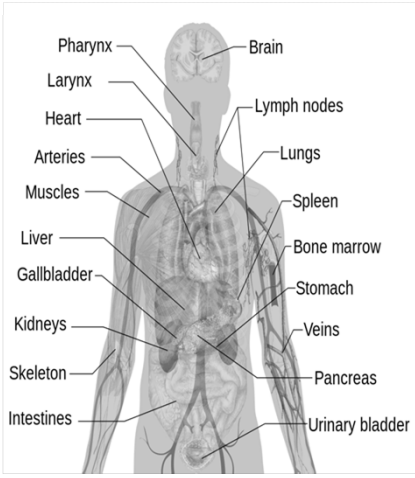
Current Immunotherapy Agents

- **PD-1/PD-L1 Inhibitors**
  - ✓ **Pembrolizumab**
  - ✓ **Atezolizumab**
  - ✓ **Durvalumab**
  - ✓ **Avelumab**
  - ✓ **Cemiplimab**
  - ✓ **Nivolumab**
- **CTLA-4 Inhibitors**
  - ✓ **Ipilimumab**

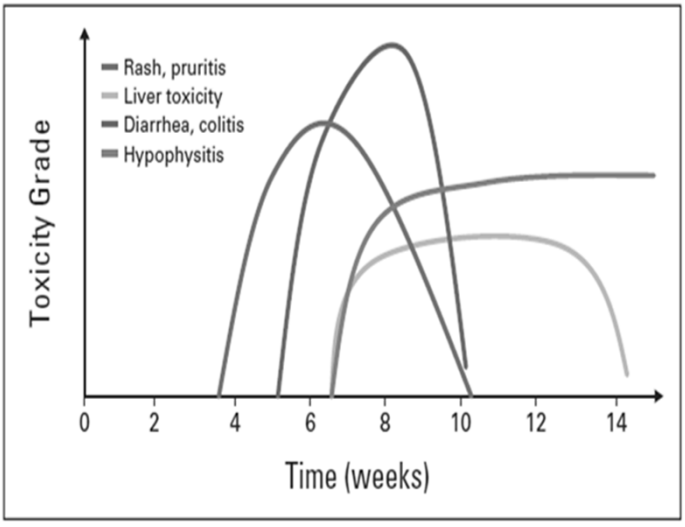


Immunotherapy Toxicity Overview

- 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 Toxicity Timing is Variable

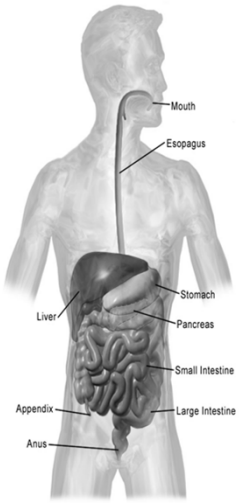


Used with Permission: Weber JS. J Clin Oncol. 2012 Jul 20;30(21):2691-7.

Immunotherapy Toxicities – General Management

Grade 1	**Mild symptoms**	Supportive measures, **Continue immune therapy**
Grade 2	**Moderate symptoms**	Supportive measures, **Hold immune therapy** <u>May</u> add steroids*
Grade 3-4	**Severe symptoms**	**Discontinue/Delay Immune therapy** <u>Add</u> steroids* or <u>increase steroid dose</u>

GI Toxicity

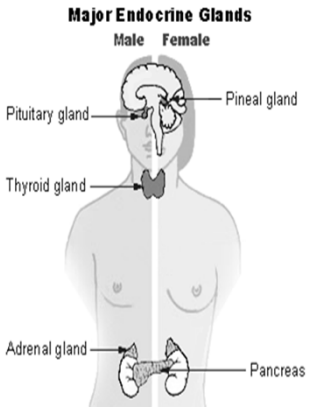


Digestive System

- **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**

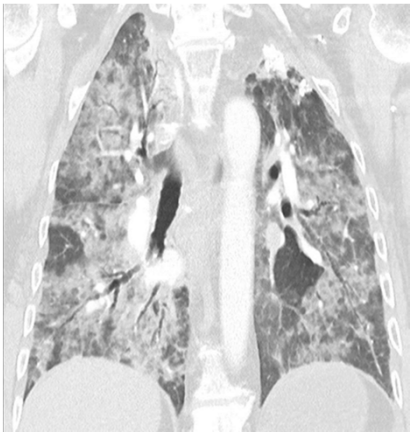
Endocrine Toxicity

- 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