Managing Complications of Chemotherapy

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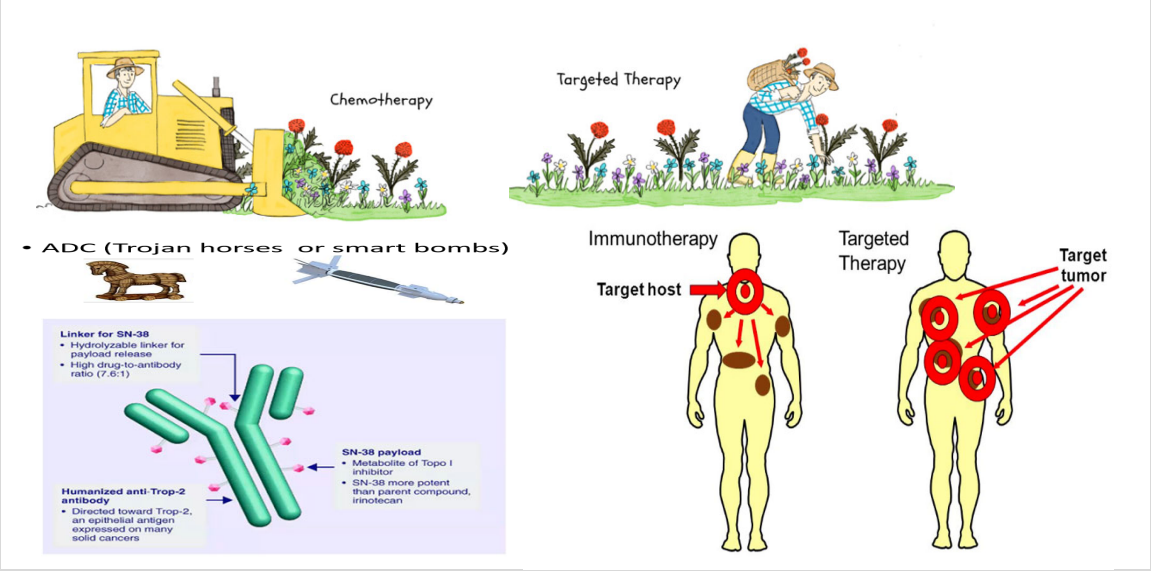
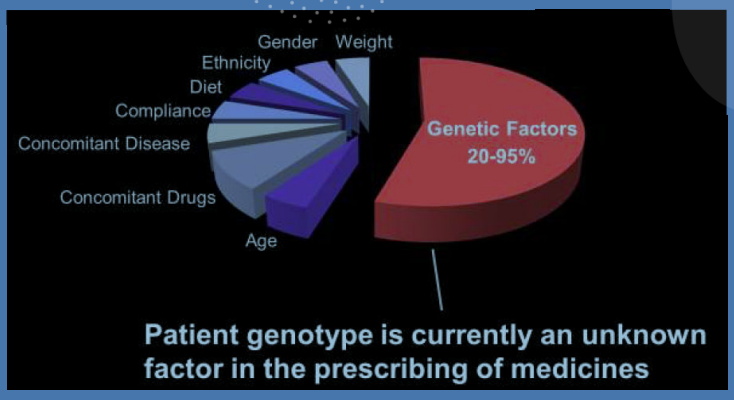
Cancer Systemic Therapies toxicities Burden

- Averse drug reactions is the 5th leading cause of death in the USA
  Highest incidence occur in older patients and those with comorbid conditions
- Over 100,000 fatal ADRs in hospitalized patients each year
- Over 2,000,000 serious ADRs in hospitalized patients per year
- Accounts for roughly 15% of all hospital admissions
- Direct cost to the healthcare system estimated at $78-177 billion annually (USA)
- A majority are underreported

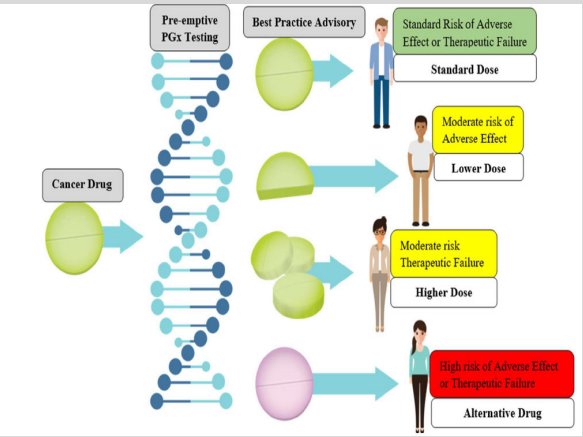
Types Of Cancer Therapeutics And How They Act



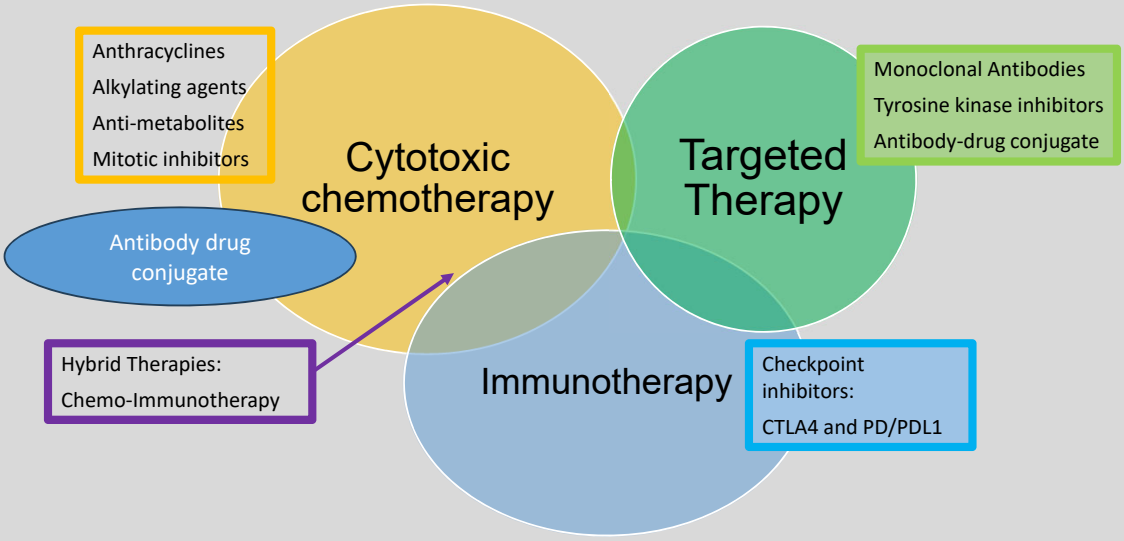
Factors influencing Drug Toxicities



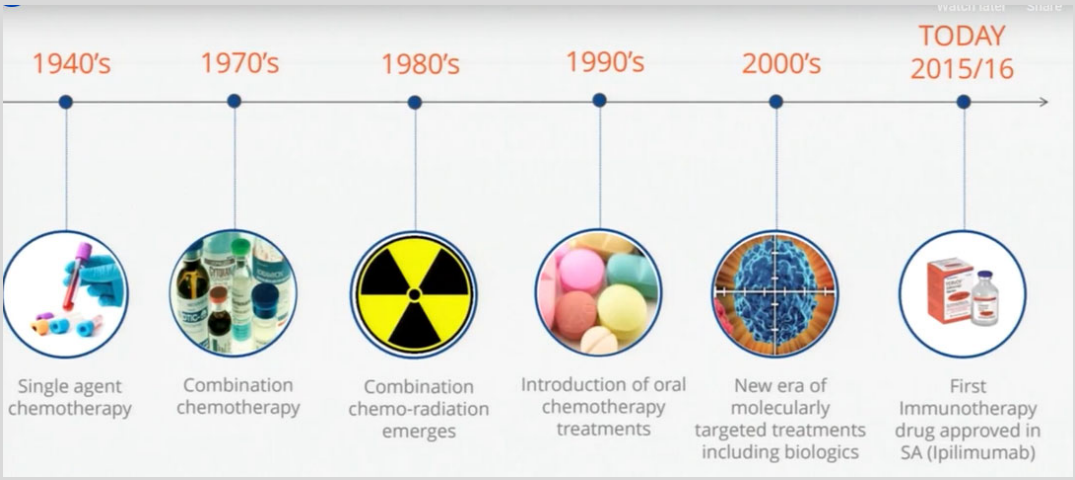
Drug response VS toxicity. can genomics be the answer to the vexing problem of Toxicity



Cancer Therapy is Evolving

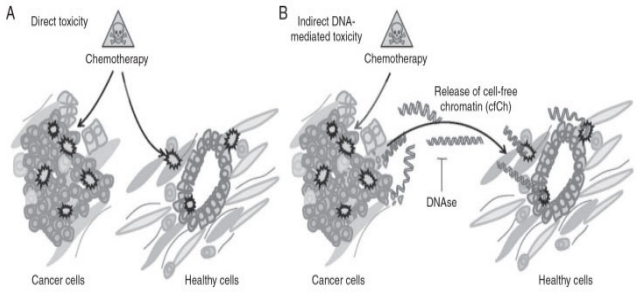


Timeline In The Development Of Cancer Chemotherapeutics



Cytotoxic chemotherapies

- GI; nausea, vomiting, constipation, diarrhea, mucositis, decrease appetite
- Neurologic: neuropathy, Memory impairment(brain fog or chemo brain), mood changes
- Cardiac:
- Hematologic; Cytopenias(anemia, leukopenia, thrombocytopenia)
- Renal(
- Skin (dry skin, rash , nail changes
- Fertility
- Immunologic(decrease immunity), allergic rxn
- Hair loss
- Pulmonary



Management and prevention

- Premedication
- Post chemotherapy medications (anti nausea, bowel regimens, appetite stimulant when necessary)
- Consider regular hydration
- Rest and light exercise
- 'cold helmet" to prevent hair loss
- Check temperature regularly and reports any symptoms/signs of infection, rigorous hygiene, avoid crowds and mask when necessary
- Eat healthy(small frequent meals), avoid spicy food or food at extreme temperatures
- Mouthwash, bland tooth paste,
- Use body creams, moisturizers

Tyrosine Kinase inhibitors

Close to 100 tyrosine kinases have been identified,

56 receptor tyrosine kinases and 32 cellular tyrosine kinases

Tyrosine kinase inhibitors (TKIs) disrupt cellular pathways regulating cancer cells growth including angiogenesis and cellular proliferation

Categorized into small molecules and macromolecules

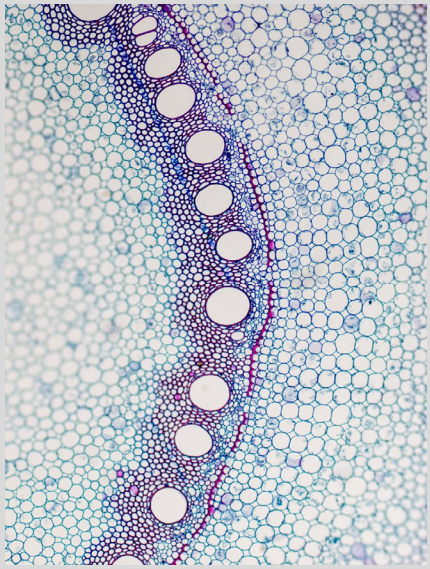
Potency, mechanism, selectivity and safety depends on selectivity of binding of various TKIs to their

Toxicities grouped into: on-target effects(through excessive inhibition of the intended TK function e.ge HTN, hypothyroidism skin reaction etc); off-target effects (simultaneous inhibition of multiple other kinases due to limited selectivity)

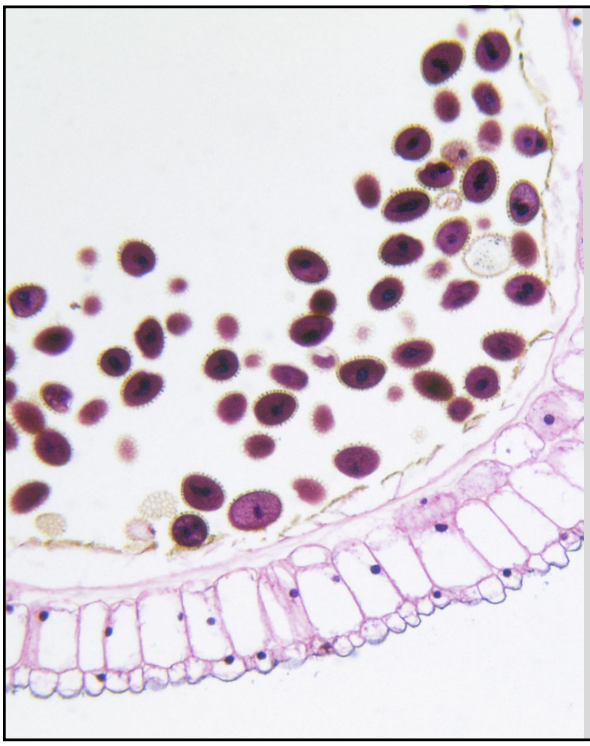
Cardiotoxicities, Risk factors and Prevention

- TKIs can adversely affect vascular endothelial cells, cardiomyocytes, signal transduction pathways, angiogenesis, microvascular function, and myocardial perfusion, arteriosclerosis, QT prolongation, arrythmia(Afib), thromboembolism, HTN, pericardial disease, PAH
- Increased ROS and decreased NO
- Type I(acute onset and progressive) and type2 (late onset, non-progressive and reversible)
- Patient-related risk factors such as CAD, advanced age, HTN,DM and smoking, obesity
- Atherothrombotic risk (circulating biomarkers such as high-sensitivity C-reactive protein, and markers of inflammation such as interleukin-1 (IL-1), IL6, and fibrinogen, cardiac biomarkers such as highsensitive troponin T, Pro PNB
- Therapy-related risk such as high-dose chemotherapy, prior anthracycline use, mediastinal radiation
- Prevention: dose reduction if EF is low, consider alternative treatment, use of anti platelets, anticoagulation, optimal BP and lipid management, counsel patients to quit smoking, lose weight, healthy diet and exercise, avoid other cardiotoxic drugs, regular surveillance with echo, EKG etc, optimal electrolyte management

Dermatology

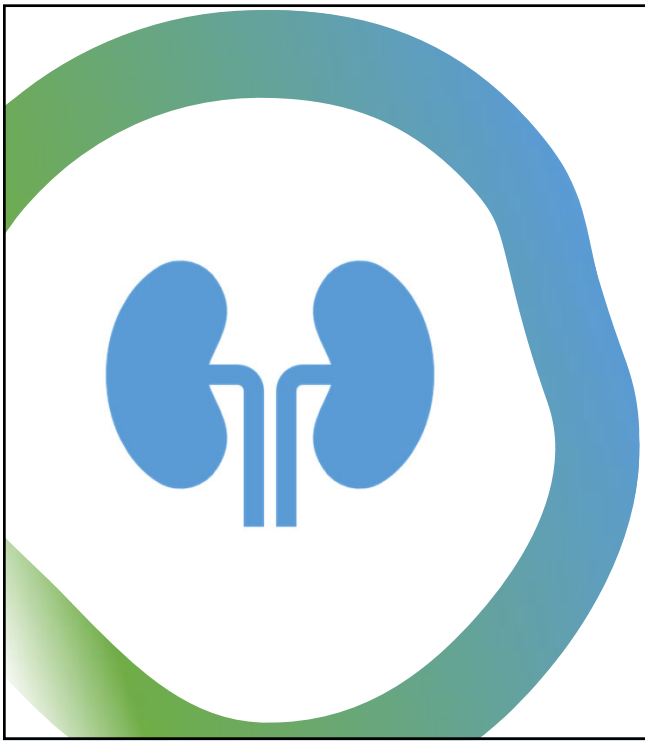


- skin reactions estimated in more than 70% of patients (severe in 2-16%) mostly in head/neck/trunk:
- Manish as rash, dry skin, pruritus, and inflammation of nail/periungual tissues
- PRIDE syndrome (papulopustular and/ or paronychia, regulatory abnormalities of hair growth, itching and dryness
- Toxicities are dose-related
- Cutaneous manifestations resulting from EGFR inhibition affect multiple molecular pathways involved in cell growth and differentiation resulting in growth arrest, decreased migration, abnormal differentiation, and stimulation of inflammatory system
- Emollient, topical steroids, topical antibiotics, dose interruption, modification and seldomly permanent discontinuation



GI Toxicities

- Diarrhea, colitis, , vomiting, stomatitis, mucositis, dysgeusia, dyspepsia, anorexia, constipation, abdominal discomfort, and weight loss, GI perforation
- EGFR-related inhibition of epithelial growth and limited healing of the GI mucosa lining, direct toxic effects on mucosal cells, increased GI inflammation
- Management : antiemetics such as Metoclopramide or ondansetron can be used as antiemetics, good oral hygiene, non-alcoholic mouthwashes, bland foods, avoid food at extreme temperatures, low fat, low-fiber diet, r/o infections, anti-diarrhea, optimal hydration, hold medication and consider dose modification



Pulmonary toxicity

- Pleural effusion, Interstitial lung disease(exact mechanism unknown ? protective function of the EGF receptors localized on type 2 pneumocyte), drug induced pneumonitis (MEK inhibitor)
- Hif2 inhibitor such as Belzultifan cause hypoxia, probably through effect on pulmonary artery vaso-constriction in response to hypoxia; usually transient but may require oxygen supplementation and dose modification; needs regular oxygen monitoring
- Pneumonitis : eg: MTOR inhibitor

Renal

- Endothelial damage leading to thrombotic microangiopathy
- Acute on chronic tubular interstitial damage
- Proteinuria /elevated creatinine.
- Drug modification, interruption, discontinuation maybe necessary
- Nephrologist consultation, ACE or ARBs
- Ocular inflammation (uveitis, conjunctivitis), retinal vein occlusion; central serous chorioretinopathy(fluid accumulation in the retinal) seen 25% patient on FGFR inhibitors, usually bilateral : self-limiting. Needs ophthalmologist

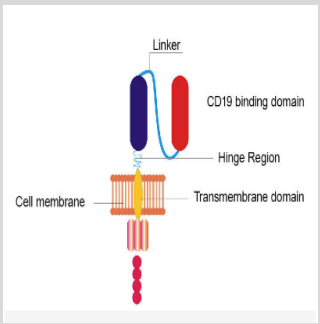
Other toxicities

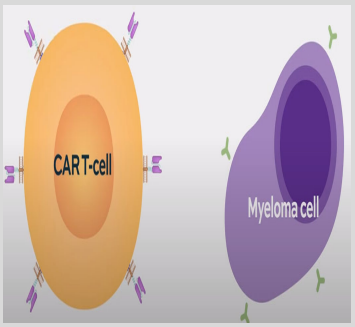
- Hepatoxicity: elevated LFTs often self limiting but may require dose modification/discontinuation depending on severity,
- Pancreatitis: VEGF inhibition results in pancreatic tissue ischemia and acute pancreatitis: often self-limiting
- Glucose metabolism: Hyperglycemia, hypoglycemia : regression of pancreatic islets, modulation of IGF-1 signaling, and decreased glucose uptake are the proposed hypotheses
- Fluid retention mostly pedal edema: may require compression stockings, diuretics, drug interruption and dose modification
- Electrolyte abnormalities
- Bone and mineral homeostasis nonspecific inhibition of TKs expressed by osteoclast and osteoblast
- Endocrinopathies; Hypothyroidism(usually subclinical), hypogonadism(rare), hypoadrenalism (rare)

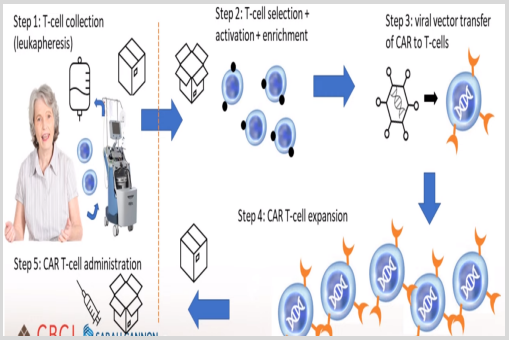
Other Toxicities, continued

- Opportunistic infections: Patients often immunocompromised, TKI also may impair macrophage function ; Pneumonia(PJP often, aspergillus fumigatus isolated), consider prophylaxis : also prone to UTI
- Cytopenia
- Neurologic side effects (cerebral infarction, arterial occlusion) rare and not reported on all studies: encephalopathies (similar to Wernicke encephalopathy) : Mechanism of action: inhibition of angiogenesis and endothelial cell proliferation leading to a slow blood flow recovery rate post-ischemia, pro-inflammation and pro-athero-thrombotic

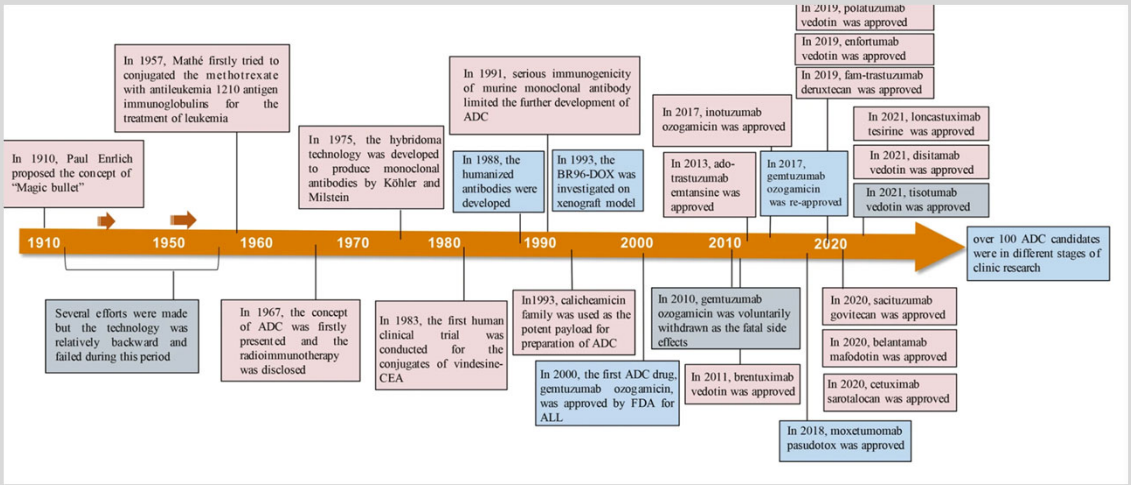
CAR T-cells



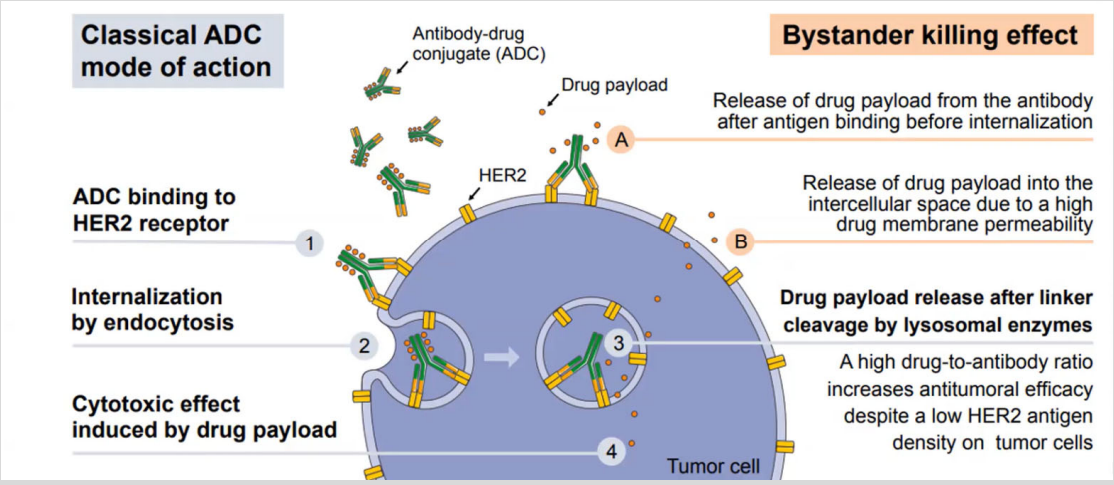




Timeline for ADC or biological missiles



ADC and side effects



Side effects (Acute -0-28 days)

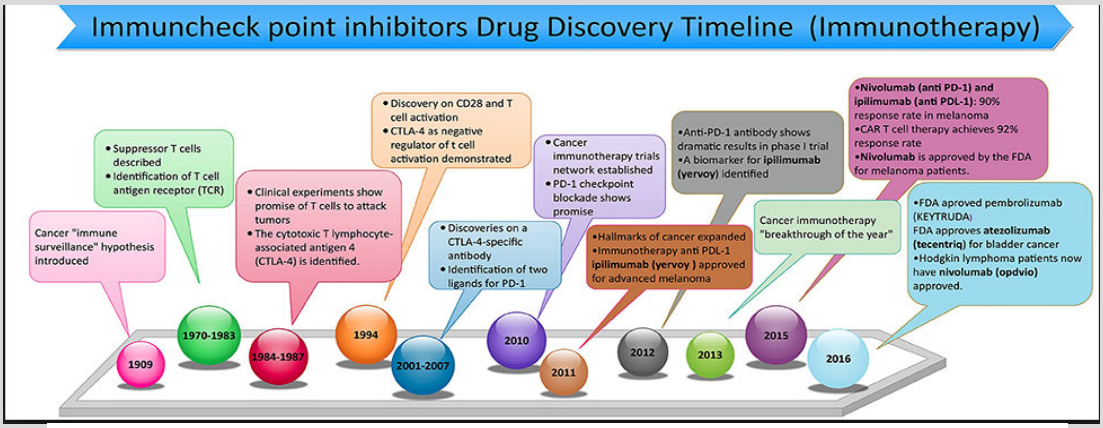
- Infections(bacterial, fungal, viral)
- Cytokine release syndrome (fever, hypotension, hypoxemia)
- grade (fever only -1; fever +hypotension/hypoxemia -2; need medication to support BP or respiratory support-3)
- Treatment Tocillizumab (anti-cytokine therapy) and steroid
  - Neurotoxicity (immune effector celll-associated neurotoxicity syndrome); tremors, memory deficit, seizures ; Tx steroid

Side effects >30 days

- Short term memory impairment, diminished reflexes (do not drive for about 2-3 months)
- Prolonged cytopenia (30%)
- Risk of infection(diminished B-cell functioning), may last up to 12 months , increase risk of shingles, PJP, URTI
- Secondary malignancy
- ? Neurologic effects

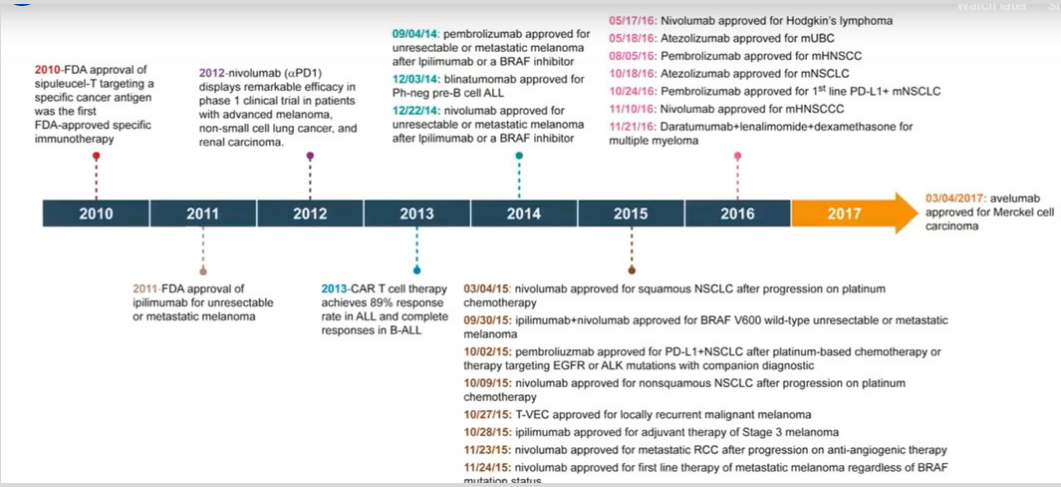
Immunotherapies

Evolution Of Cancer Immunotherapy(Checkpoint inhibitors)

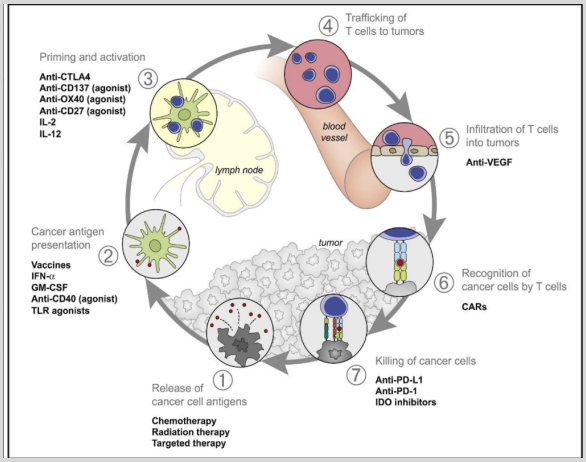


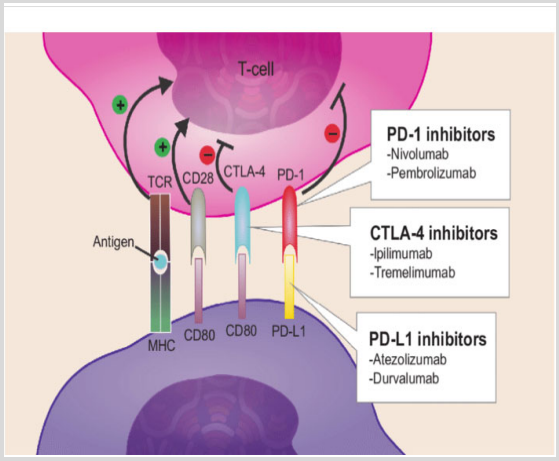
Curtesy of Hashem et al, Frontiers in pharmacology

FDA timeline for immunotherapy approval



Immune Checkpoint Inhibitors

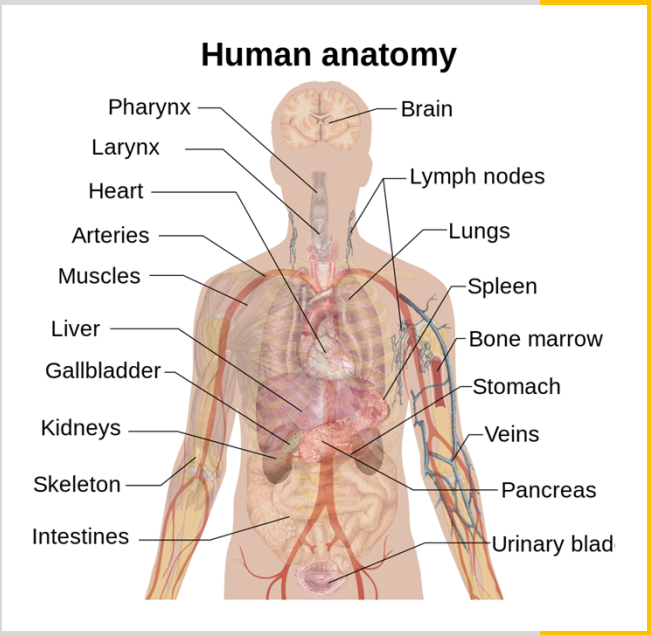




Courtesy Hong Li-Want et all, molecules 2022

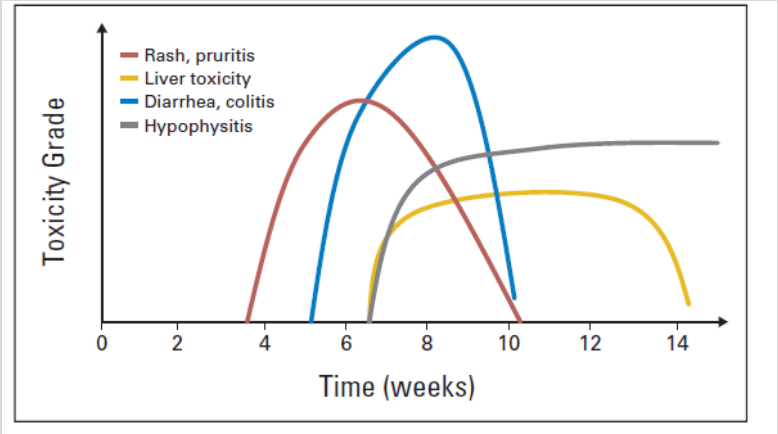
Immunotherapy Toxicity Overview

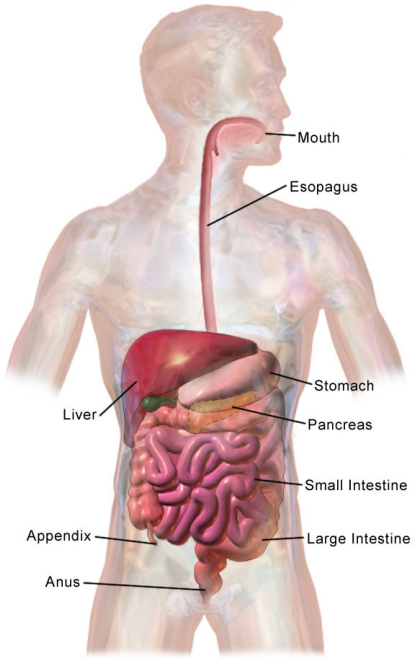
- Autoimmune toxicity may affect any organ system
- May mimic other conditions
- Common Toxicities (≥ 10%)
  - Fatigue(16-26%)
  - Rash/pruritis
  - Diarrhea(30%)
- Uncommon Toxicities (< 10%)
  - Hepatitis
  - Pneumonitis(1-5%)
  - Endocrinopathies
  - Cardiac
  - Pancreatitis/ DM1
  - Renal (1-5%)
  - Infusion rxn
  - Neurologic



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

Immunotherapy Toxicity Timing is Variable





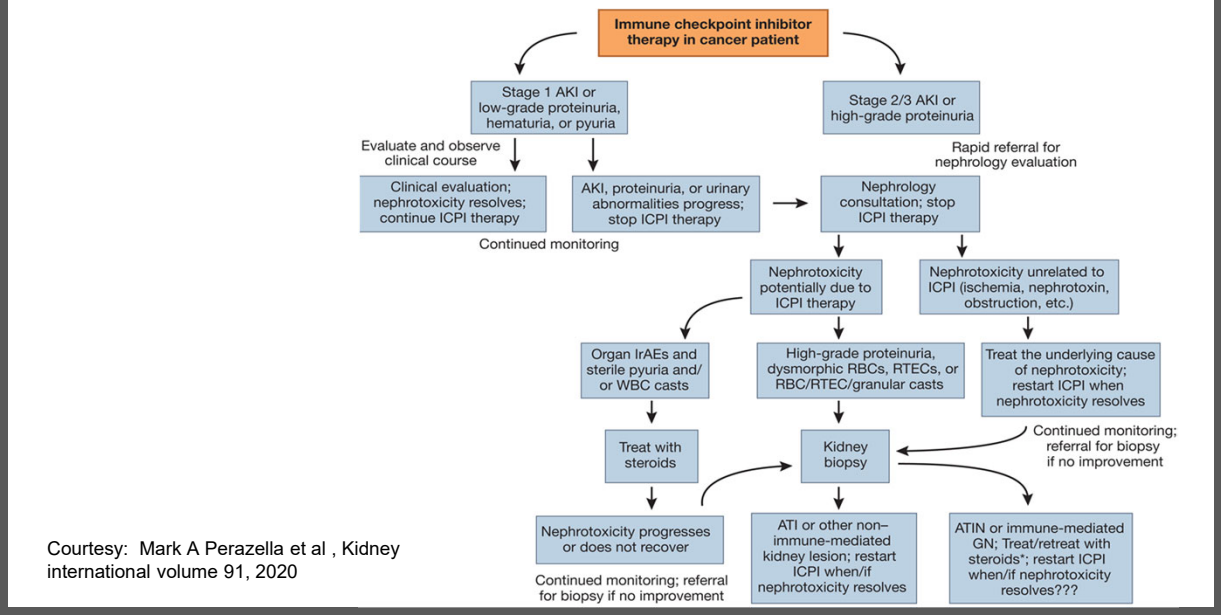
Digestive System

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

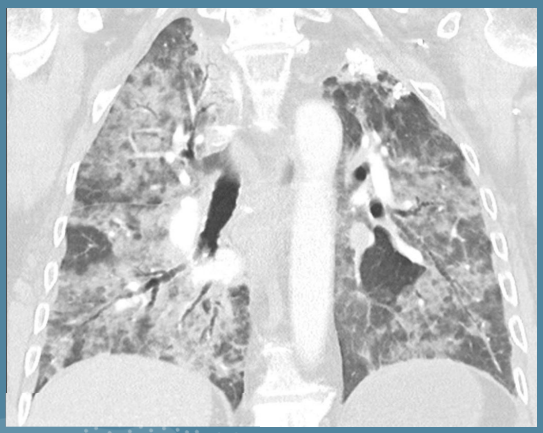
Renal Toxicities

- Acute tubular interstitial nephritis/ allergic nephritis(fever, rash, proteinuria, eosinophilia and eosinophiluria
- Acute tubular necrosis , crystal nephropathy, tubular atrophy, interstitial fibrosis
- Minimal change disease
- Membranous glomerulonephritis
- Necrotizing glomerulonephritis
- Focal segmental glomerulonephritis
- C3-Glomeruloneprhitis



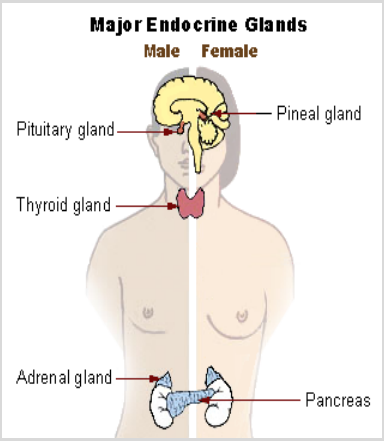
Courtesy: Mark A Perazella et al , Kidney international volume 91, 2020

Pulmonary Toxicity -Pneumonitis

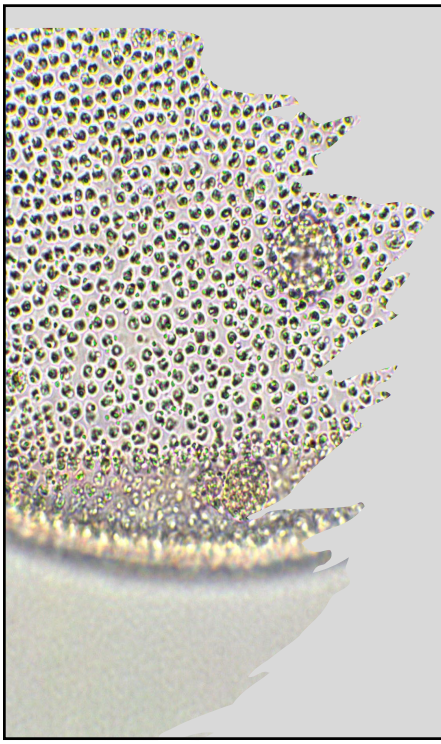


- Focal or diffuse inflammation of lung parenchyma
- Onset may be early or late
- Differential includes infection, COPD exacerbation, and disease progression
- Bronchoscopy may be helpful if patient is stable
- Empiric therapy: Steroids and antibiotics

Endocrine toxicity

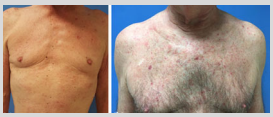


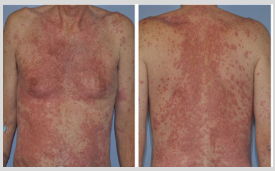
- Thyroid dysfunction (>10%)
  - Replacement therapy for hypothyroidism
  - Symptom control for Hyperthyroidism
- Hypophysitis (<5%)
  - Non-specific symptoms: headache, fatigue
  - Cortisol, ACTH, thyroid function testing
- Adrenal insufficiency (rare)
  - Dehydration, hypotension, hyperkalemia, hyponatremia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

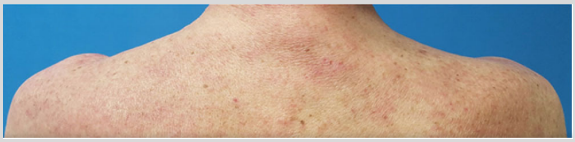


Skin Toxicity

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







Pictures of Skin Toxicities

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

Principles of Management

- Depend on severity and organ system affected
- For mild severity: withhold ICI, r/o other causes and monitor the patient closely until symptoms resolve
- Moderate severity: In addition to above, treat with steroid, other medications to control symptoms and replacement therapy; usually in the outpatient setting
- Severe cases: prompt hospital admission, stabilize the patient, IV steroid & othe supportive care
- ICI can be re-introduced in some cases
- *steroid are the workhorse of ICI toxicity management, dose and duration depend on severity
- ** other immune modulators such as Rituximab, IVIG, Infliximab and mycophenolate etc. maybe required
- Other supportive medications such as NSAIDs, gabapentin maybe indicated
- PCP prophylaxis maybe required depending of duration of steroid taper

Immunotherapy Toxicities – General Management