Clinical Oncology

Clinical Evaluation, Staging, Chemotherapy

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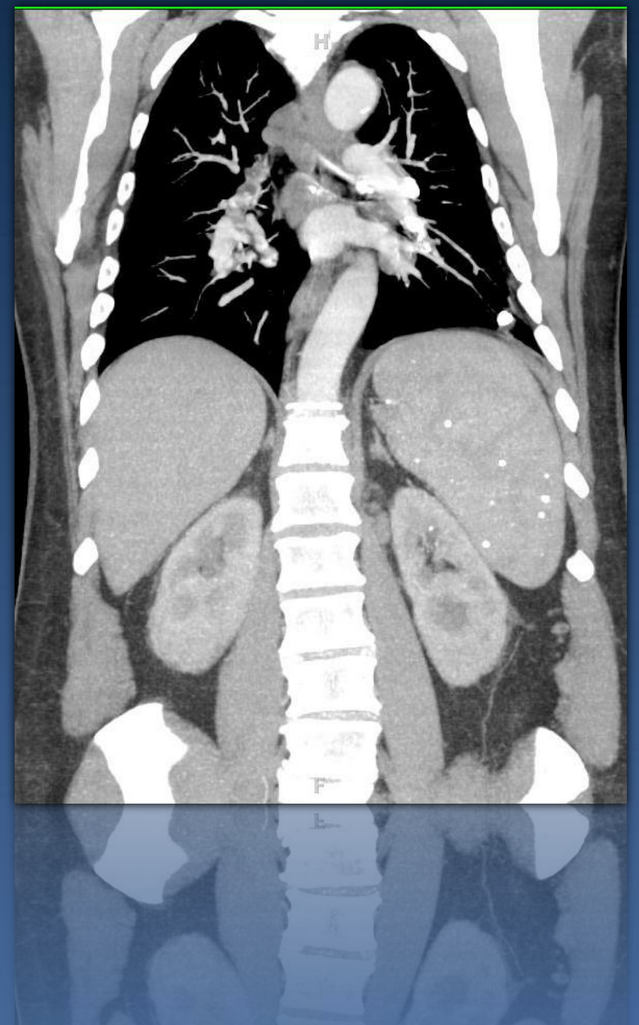
Mass Effects of Malignancy

- Tumors produce clinical problems as a result of local expansion, with obliteration of normal tissues, as the malignant cells proliferate within the confines of the involved organ
- Treatment of these mass effects centers upon treatment of the malignancy causing the symptoms



Paraneoplastic Syndromes

- Factors released by the tumor into the blood cause clinical symptoms
- The optimal treatment for paraneoplastic syndromes is treatment of the underlying malignancy
  - Review…
    - Eaton Lambert Syndrome
    - SIADH
    - Hypercalcemia
    - Erythrocytosis

Weight Loss and Malnutrition

- Weight loss associated with anorexia is a frequent problem in cancer management. It is often the presenting sign of malignancy
  - The wasting which results is known as ***cachexia***
  - The cause for cachexia remains to be determined but might be attributed to circulating factors…
    - Cachectin (tumor necrosis factor or TNF)—protein that can cause cachexia in laboratory animals and has been found in high levels in patients with advanced cancer
    - Proteolysis-inducing Factor (PIF)—found in serum and urine of cachectic cancer patients

Weight Loss and Malnutrition

- Potential causes…
  - Abnormalities of taste and smell
  - Physiologic malfunction of the gastrointestinal tract
  - Excessive energy demands made by the tumor
  - Failure to adapt energy expenditure to the levels of nutrient intake
- Treatment…
  - Underlying disease
  - Megesterol acetate (Megace®)
  - Dronabinol (Marinol®)

Fever

- Usually attributable to infection
- Types of infection may be unusual due to cancer-related debility and granulocytopenia from treatment
- Infection by endogenous organisms must be considered
- "Tumor fever” - due to increased circulating levels of interleukin-1 (endogenous pyrogen)

Hematologic Abnormalities

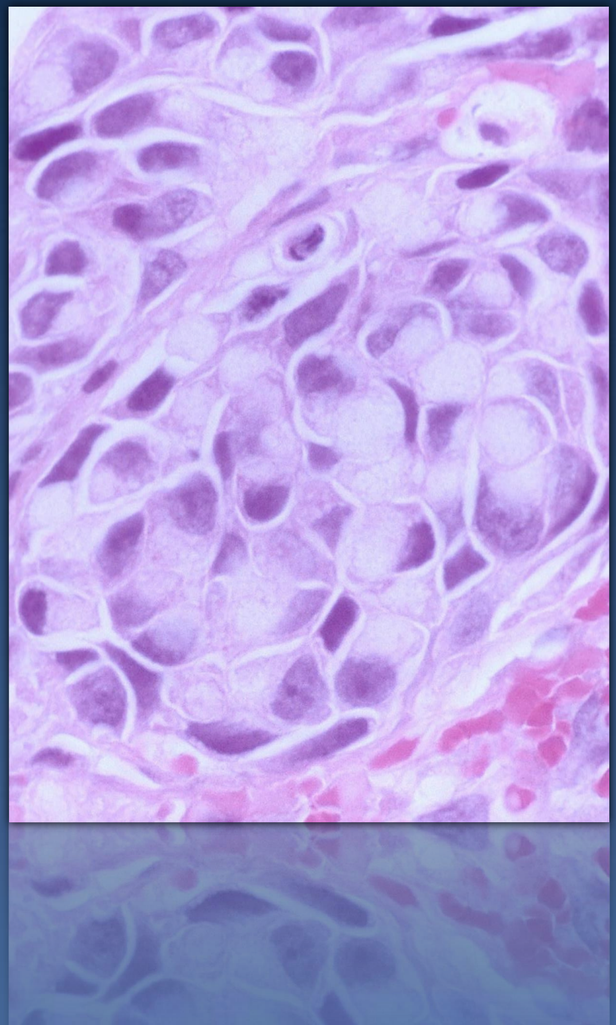
- Anemia
- Granulocytopenia
- Thrombocytopenia
- Coagulopathies

Anemia

- Frequent in advanced stages of malignancy
- Increased destruction of erythrocytes can result from hypersplenism, microangiopathic hemolysis, and autoantibodies seen especially in the lymphoproliferative malignancies
- Anemia due to bleeding is one of the cardinal findings of gastrointestinal malignancies
- Nutritional deficits may result in decreased red cell production
- The anemia of chronic disease is often present

Granulocytopenia & Thrombocytopenia

- Commonly associated with marrow infiltration
- Chemotherapy



Coagulopathies

- Mucin-producing adenocarcinomas most frequent cause
- Trousseau's syndrome-migratory thrombophlebitis, which can produce venous thrombosis and pulmonary embolism
- Hypercoagulable states may be associated with marantic (nonbacterial) endocarditis and resultant thromboembolic episodes

Coagulopathies

- Treatment of the primary malignancy is the only successful therapeutic attack on the problem
- Low molecular weight heparin is standard treatment for thromboembolic disease in face of malignancy

Clinical Evaluation

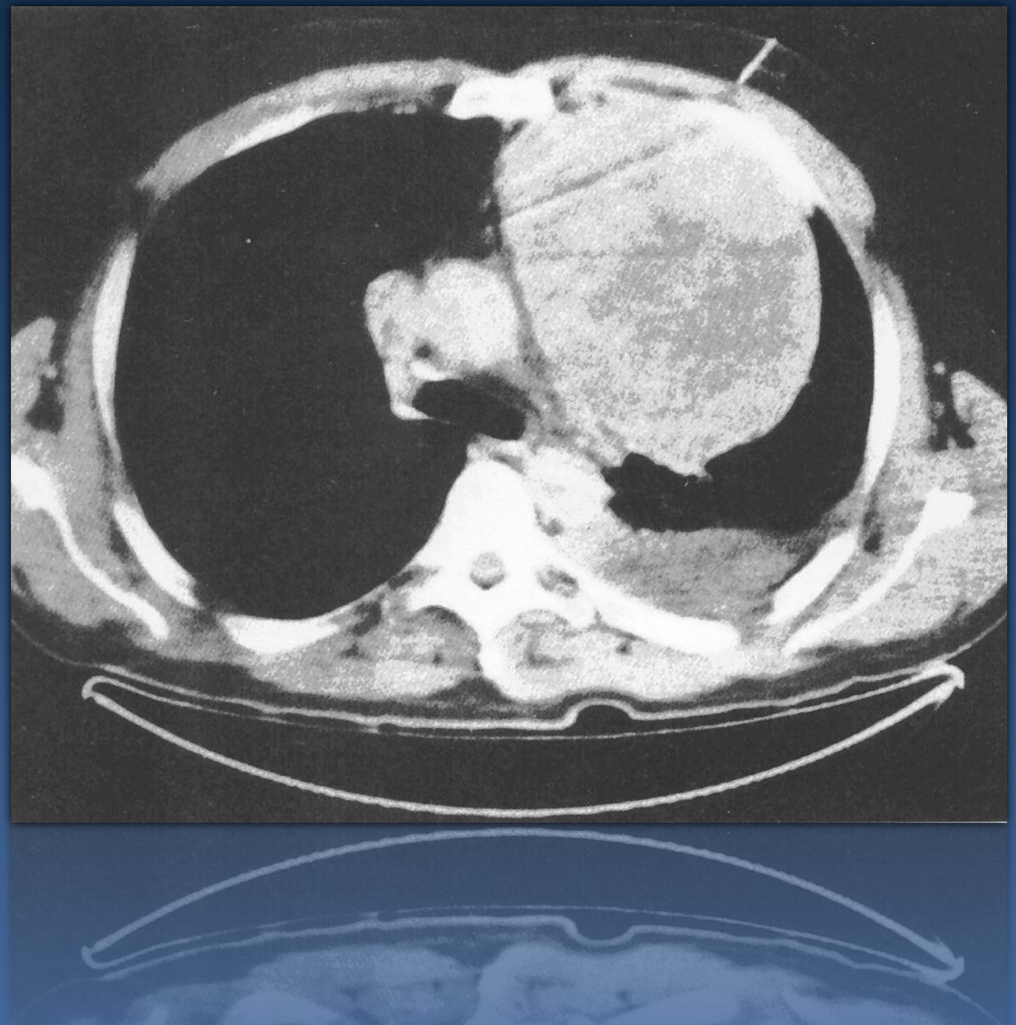
- Three general goals…
  - Biopsy of tissue to establish a diagnosis
  - Determine the extent of tumor spread (staging)
  - Determine the effects of the malignancy on the health and performance of the patient (***performance status***)

Cancer Screening

- Four diagnostic screening tests have proved of value in early cancer detection:
  - The exfoliative cytology (Pap smear) screen for cervical cancer
  - Fecal occult blood testing, accompanied by periodic sigmoidoscopy
  - Mammograms
  - Digital rectal exam with PSA for prostate cancer
    - Recent US Preventive Service Task Force recommendation is to avoid screening PSA in men at low risk…there is considerable debate over this recommendation!

Pathologic Diagnosis

- Essential to exclude nonneoplastic disorders
- May involve a surgical operation, local incision, or removal of tissue under direct visualization (bronchoscopy, colonoscopy). In some cases, fine needle aspiration (FNA) of tumor cells can be performed



Staging of Cancer

- Anatomic extent of the tumor in its primary location and in metastatic sites. Reasons to state patients include…
  - Optimal treatment plans based on disease stage
  - Provides information to better evaluate the prognosis
  - Determines disease extent accurately for evaluating factors influencing the results of new treatments for cancer

Staging—The TNM System

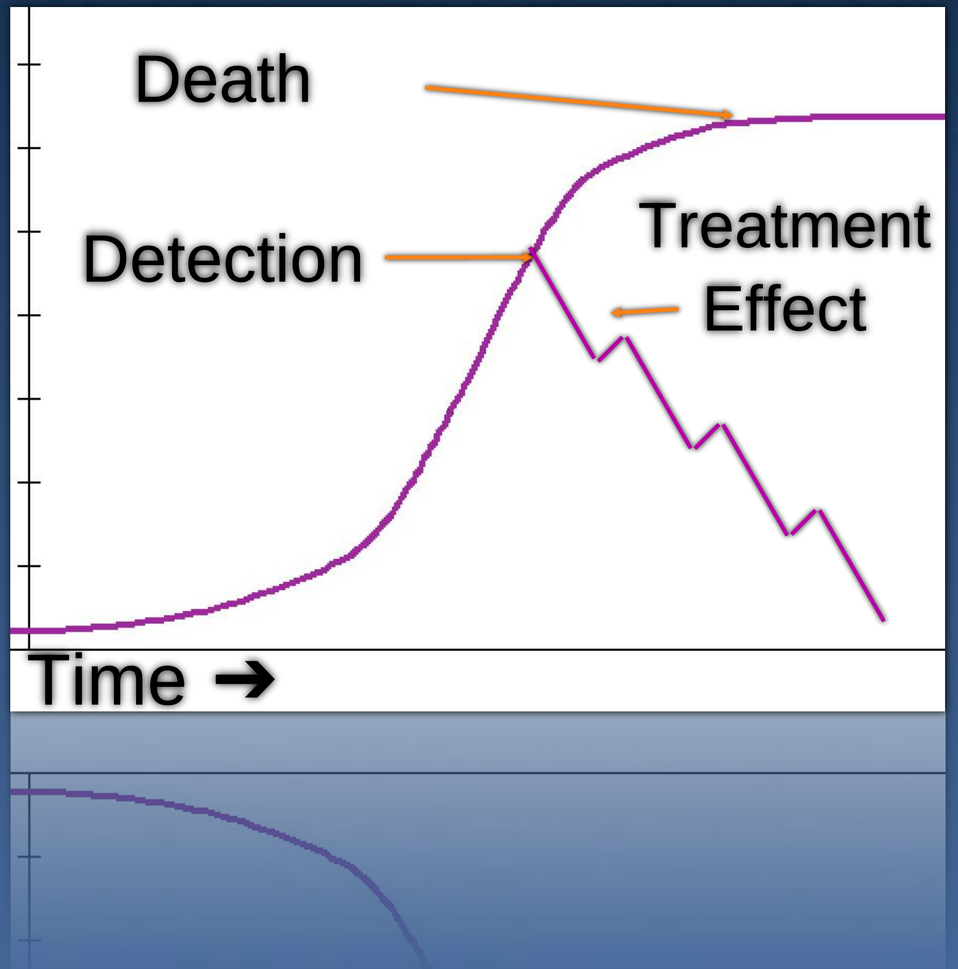
- Three elements are characterized…
  - Size of primary tumor (T)
  - Involvement of regional lymph nodes (N)
  - Presence or absence of metastases (M)
- Malignancies are then placed into stages (I thru IV) based upon the individual TNM state
  - In general, patients with lower stage numbers (I and II) have less widespread disease than patients with higher stage numbers (III and IV)

Chemotherapy

- The Cell Cycle
- Classes of Chemotherapeutic Agents
- Complications of Chemotherapy
- Newer Chemotherapeutic Agents

Biology of Tumor Growth

- Gompertzian kinetics: as the mass increases, exponential retardation of growth occurs
- Tumor doubling time (the time required for doubling tumor volume) is influenced by the cell cycle time, the fraction of cells undergoing cell division, and the rate of cell loss from the mass
- Average number of divisions for cancer to become clinically apparent = 30 ($1x10^9$ cells)
- Average number of divisions for cancer to be lethal = 40 ($1x10^{12}$ cells)
  - A cancer has lived 75% of its lifespan when detected!

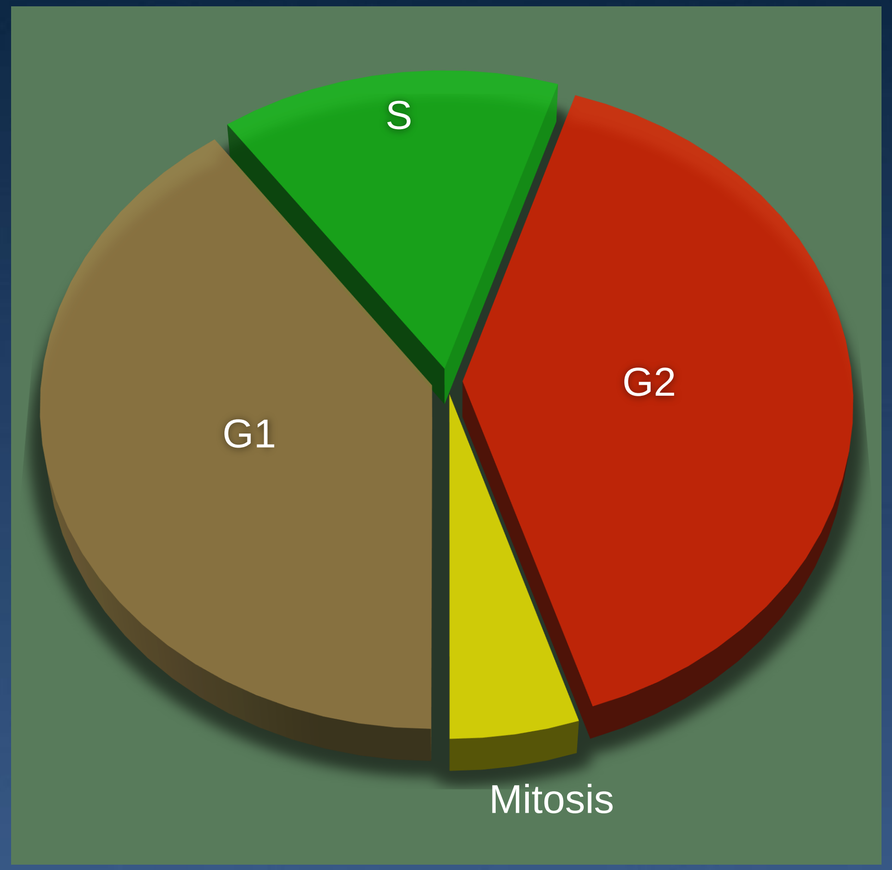


The Cell Cycle and its Role in Chemotherapy

- Current knowledge of cell growth suggests that there are two discernible periods of importance…
  - Mitosis—when separation of nuclear material and cytoplasm occurs, resulting in two identical cells
  - The duplication of nuclear material (the S phase)

The Cell Cycle and its Role in Chemotherapy

- Additionally, the remainder of time is divided into two phases, G_1 and G_2
- The entire period of time from one cell division to the next is called the cell cycle
- Chemotherapy affects cells in direct relationship to how active they are in the cell cycle



The Cell Cycle and its Role in Chemotherapy

- Two general classes of drugs—cell cycle specific (only effective while malignant cells are in a certain point in the cycle) and cell cycle nonspecific (effective at any point in the cell cycle)
- Other classes (hormones, biological agents) have complex and poorly understood mechanisms of action

Classes of Drugs

- Alkylating agents
  - Bind directly to DNA and cause cross-strand breaks which disrupt transcription and replication
  - Mechlorethamine, cyclophosphamide, nitrosoureas, and platinum derivatives are examples
  - Most are cell cycle nonspecific

Classes of Drugs

- Antimetabolites
  - Compete with normal precursors for the catalytic site of key enzymes or substitute for metabolites that are incorporated into DNA or RNA
  - Methotrexate, pemetrexed, 5-FU, Ara-C, gemcitabine, 6-MP, 6-TG are examples
  - Most are cell cycle specific

Classes of Drugs

- Antibiotics
  - Intercalate with DNA causing inhibition of transcription and replication, also inhibit topoisomerase II
  - Doxorubicin (Adriamycin), daunorubicin, actinomycin-D, and bleomycin are examples
  - Cell cycle nonspecific

Classes of Drugs

- Plant alkaloids
  - Vincristine, vinblastine, vinorelbine, vindesine
    - Bind to tubulin, causing impairment of microtubule formation
  - Etoposide (VP-16)
    - Inhibits topoisomerase II, causing single strand breaks in DNA
  - Cell cycle specific

Classes of Drugs

- Hormonal agents
  - Tamoxifen—binds to (and blocks) estrogen receptors
  - Leuprolide, goserelin—LHRH agonists which decrease secretion of LH and decreases sex hormone production
  - Flutamide, bicalutamide—binds to (and blocks) testosterone receptors
  - Aromatase inhibitors (anastrozole, exemestane, letrozole)—decrease sex hormone production by adrenal gland

Classes of Drugs

- Biological agents
  - Interferons—mechanism unclear
  - Interleukins—mechanism unclear
  - Epidermal growth factor inhibitors
    - Erlotinib (Tarceva®); minimally effective in NSCLC
    - Cetuximab (Erbitux®); effective in lung, head/neck, colorectal cancers (*K-RAS* wild type only)
  - Tyrosine kinase inhibitors—imatinib (Gleevec®) effective in CML and GI stromal tumors

Classes of Drugs

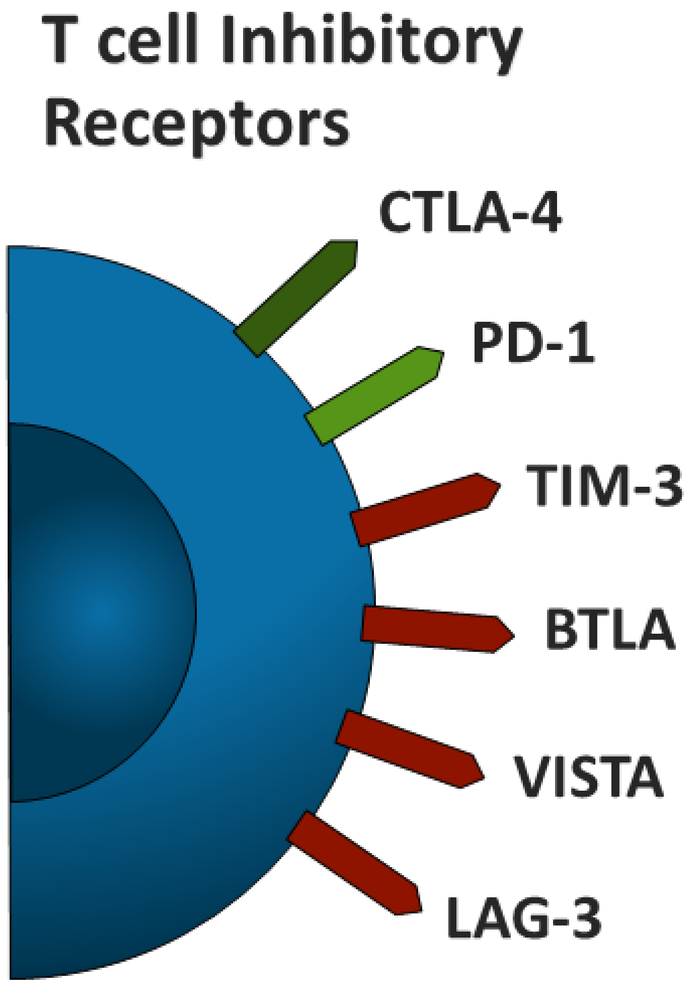
- Monoclonal antibodies
  - Targeted therapy intended to direct immune system at malignancy
  - Rituximab (Rituxan®)—directed at CD20 on lymphocytes and effective in lymphomas, CLL
  - Cetuximab (Erbitux®)—directed at epidermal growth factor receptor and affects tyrosine kinase activity; effective in colorectal Ca and others
  - Alemtuzumab (Campath®)—directed at CD52 on lymphocytes and effective in CLL
  - Other agents tagged with radioisotopes (Zevalin®, Bexxar®) used in refractory lymphomas

Classes of Drugs

- New targeted therapies
  - CTLA-4 - Ipilumumab
    - Useful in melanoma
  - PD-1/PD-L1 - Nivolumab, Pembrolizumab
    - Useful in NSCLC and emerging in other areas

Immune Checkpoints and Cancer Therapy

http://www.medscape.org/viewarticle/844988



- Key immune checkpoints that regulate the immune response
  - CTLA-4 (activation step of the immune response)
  - PD-1 (effector step)
- Anticancer therapies developed against CTLA-4 and PD-1 and its ligands
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab

Disis ML. *Semin Oncol*. 2014;41:S3-S13.[7]

Complications of Chemotherapy

- In general, chemotherapy tends to affect cells that grow rapidly, whether normal or abnormal
- Constitutional complaints…occur to some degree in over 90% of patients
  - Fatigue, weakness, lassitude ("flu-like")
  - Anorexia—difficult to tell in some cases whether it is secondary to drugs or cancer

Gastrointestinal

- Alkylating agents and antimetabolites are primary culprits
- Nausea/vomiting—very uncommon with newer antiemetics
- Diarrhea—may potentially occur to some degree with most agents, especially 5-FU, methotrexate
- Mucositis—painful mouth sores (stomatitis) not related to infectious agent, but may involve the entire gastrointestinal tract
- Hepatitis B virus reactivation reported with anti-CD20 antibodies; contraindicated in patients with a history of HBV infection!

Respiratory

- Occurs most commonly with busulfan, bleomycin, mitomycin-C
- Pulmonary fibrosis is the usual pathologic problem
- PFT's almost always abnormal (especially DLCO)
- "Radiation recall"…interstitial infiltrates in regions of lung previously irradiated when subsequent chemotherapy (especially Adriamycin) is used

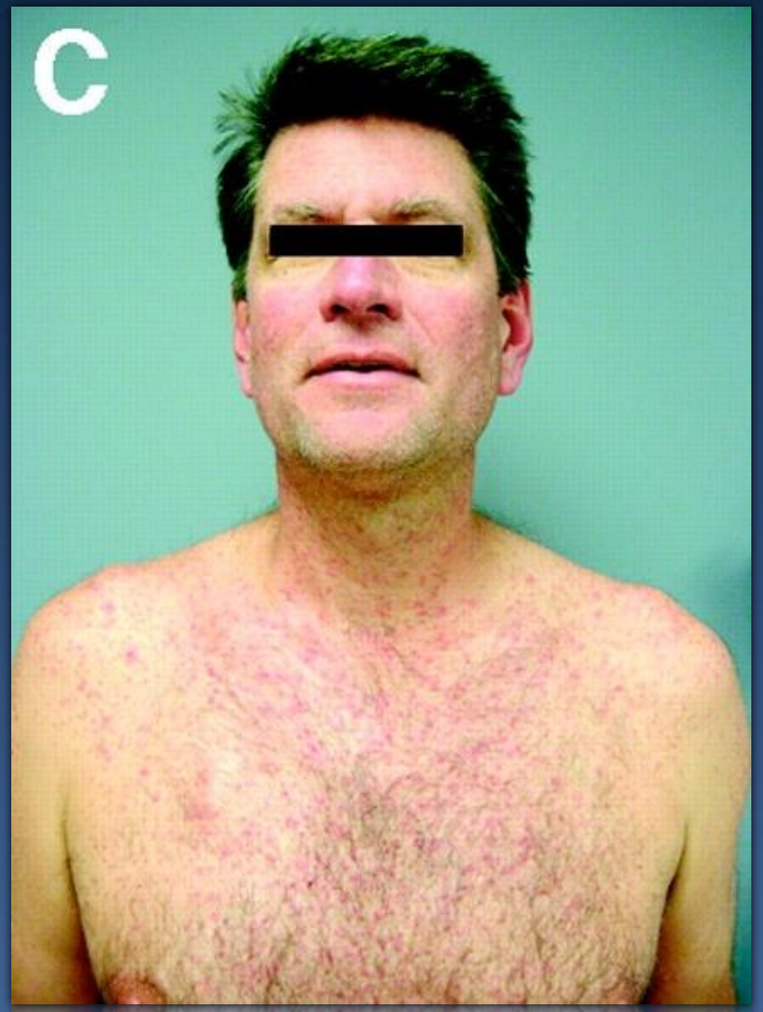
Dermatologic

- 5-FU, cisplatin, Adriamycin all sensitize skin to sunlight and increase risk for sunburn
- "Hand-Foot syndrome"…most commonly with 5-FU, hands and feet become painfully swollen, with subsequent desquamation
- Acral erythema…tips of digits become erythematous and painful, occurs with Ara-C, 5-FU

Hand-Foot Syndrome

Dermatologic

- Rash
  - Can occur with targeted therapies known to affect the epidermal growth factor receptor (EGFR) pathway
  - imatinib, gefitinib, erlotinib, cetuximab, others



Genitourinary

- Platinum containing agents are all nephrotoxic (cisplatin more than carboplatin)
- Cyclophosphamide (in high dose) and ifosfamide (at any dose) may cause hemorrhagic cystitis
- Toxicity is curtailed/avoided with vigorous hydration (for all the above), mannitol diuresis (for platinum compounds), and the use of mesna for ifosfamide

Neurological

- Seizures—reported with high dose busulfan
- Paresthesias/dysesthesias/hyporeflexia—

  Reported with vinca alkaloids, cisplatin, taxanes
- CNS disturbances—psychoses, hallucinations, leukoencephalopathy
  - Rare, but are increased in frequency with CNS chemotherapy, combined radiation and chemotherapy, anti-CD20 monoclonal antibodies

Hematologic

- The most frequent delayed complication (5 days or more after chemo.)
- Anemia, leukopenia,thrombocytopenia— can occur with any single agent and with most combination agents
- The possibility of neutropenic fever, bleeding, or anemia exists for EVERY PATIENT WHO RECEIVES CHEMOTHERAPY
- Neutropenic fever is a medical emergency!

Hematologic

- Supportive care minimizes the risk involved
- Hemolytic-uremic syndrome— mitomycin-C, risk is dose related and cumulative; most die, plasmapheresis may be helpful in some cases

Endocrine

- Hypophysitis
  - Can occur with ipilumumab
- Hypothyroidism
  - PD-1/PD-L1 directed agents

Other

- Fever—VP-16, interferons, interleukins are common culprits
- Extravasation—drugs leak outside of the vein and cause local tissue damage, increase the risk of infection, and may result in amputation
  - Most common with agents known as vesicants (Adriamycin, methotrexate)
  - Most agents known to cause local tissue damage on extravasation are given by central vein