

New Topics

- HTLV (Human T Lymphotropic Virus) single-stranded RNA retrovirus (similar to HIV) that causes T-cell leukemia/lymphoma, demyelinating tropical spastic paraparesis (ataxia, incontinence, etc), *Strongyloides stercoralis* hyper-infection, etc, but note that only 4% of seropositive pts develop these diseases
- Normally PET avid areas include brain/heart/kidneys
- advances in cancer not great but...
 - curative intent for childhood leukemia, lymphoma, testicular cancer
 - better supportive meds ie anti-emetics
 - better scheduling/dosing of chemo
- Langerhan's Cell Histiocytosis aka Histiocytosis X
 - Def: Heterogenous group of disorders characterized by proliferation of Langerhan cells (phagocytic/antigen-presenting dendritic cells from BM) and are located in epidermis
 - S/S: varied from indolent to very aggressive
 - Types: (1) Eosinophilic Granuloma: single benign painful bone lesion on skull/femur, (2) Hand-Schuller-Christian Disease: chronic dz in infants w/ skeletal lesions + diabetes insipidus + exophthalmos, (3) Letterer-Siwe Disease: vast disease affecting skin/liver/spleen/LN/BM/lungs resulting in sepsis in infants

General Onc

- Definition
 - Hyperplasia (increase number), Metaplasia (change in cell type), Desmoplasia (tumor induced proliferation of fibrous connective tissue)
 - Anaplasia (more primitive/undifferentiated in nature w/ hyperchromatic nuclei, increase N/C ratio, etc)
 - Grade (histologic appearance from I (well-differentiated) to IV (poorly-differentiated))
 - Dysplasia (loss of orientation/shape/size aka preneoplastic) to Neoplasm
 - TNM Stage (Tumor-size/LN/Mets) more prognostic value than grade
- Normal Cellular Stages
 - **Proliferation:** G₀ (Quiescence where cell is doing its normal intended function) + G₁ (synthesizing protein for S) + S (DNA Synthesis) + G₂ (synthesizing protein for M) + M (Mitosis)
 - Specific Regulatory Points: G₁/S regulated by Cyclin D/E and G₂/M regulated by Cyclin A/B, NB cyclins activate Cyclin Dependent Kinases (CDK) which subsequently phosphorylate proteins which trigger cell cycle transitions, NB there exists CDK inhibitors termed p# (14,15,16,18,21,27,etc)
 - General Regulation: growth factors bind transmembrane receptors (tyrosine kinases, G-proteins, etc) allowing malignant cells to grow and extracellular molecules bind extracellular matrix (proteoglycans, etc) and cell-cell adhesion molecules (integrins, cadherins, selectins, etc) allowing malignant cells to be invasive
 - **Differentiation:**
 - **Senescence:** all cells can only replicate a number of times based on the shortening of Telomeres at the end of DNA which each replication, at a critical length cells are no longer able to replicate, some cancers have activate Telomerase which adds length to Telomeres
 - **Programmed Cell Death aka Apoptosis:**
 - Exogenous Signals (eg radiation, hypoxia, etc) → ↑p53 → ↑bax/bak → ↑Apoptosome → ↑Caspase 3 → Cell Death
 - Endogenous Signals (eg) → ↑TNF-R1/Fas/DR5 → ↑Caspase 8 → ↑BID → ↑Apoptosome → ↑Caspase 3 → Cell Death
 - NB there exists inhibitors of this pathway (bcl, FLIP, FLICE, TNF-R)
- Genetic (10%) + Environmental Factors (90%) that lead to malignant transformation
 - General Mechanism: environmental/extracellular factors stimulate cell turnover, increase r/o somatic mutations, etc → once a mutation has occurred subsequent incremental ones occur in non-linear multistep fashion until a threshold is passed after which a cell becomes malignant
 - Environmental/Extracellular Factors (1) epigenetics aka modification of DNA by environmental factors like methylation suppression or acetylation activation, (2) direct carcinogens, (3) high omega-6 and low omega-3 affecting NF-Kappa-B inflammatory pathways, (4) oxidation pathways
 - Chemical Carcinogens (diet, tobacco, radiation, viral antigens)
 - Chronic Inflammation (IBD, infection etc)
 - Genetic Factors
 - Activating Mutations of **Proto-Oncogenes (OG)**
 - Growth Factors in Extracellular Space: Wnt, Sis, IGF, EGFR, etc
 - Signal Transducing Proteins in Cell Membrane: K-ras, B-raf, etc
 - Kinases in Cytoplasm: HER2, Neu, ERB2, etc
 - Transcriptional Regulatory Proteins in Nucleus: c-Myc, etc
 - Deactivating Mutations of **Tumor Suppressor Genes (TSG)** (Knudson's double hit hypothesis via loss of heterozygosity, allele deletion or transcriptional silencing via CpG methylation, one mutant allele can exist at birth or pt unfortunately gets two mutations during life): p53, p16, APC, DPC4/SMAD4, E-Cadherin, Rb, BRCA2, Axin, LKB1
 - Deactivating Mutations of **DNA Repair Genes**

- Microsatellites (during DNA synthesis error occurs slippage at microsatellites which are regions of mono/dinucleotides creating a milieu for permitting further mutations in OG/TSG that contain microsatellites) hMSH2,3,4,5,6, MLH1,3, PMS1,2
 - Oxidative Damage: (oxidation damages guanine nucleotides) MYH
 - NB you also need Neo-Angio/Lymphangiogenesis (VEGF, bFGF, TGF-alpha), Epithelial-Mesenchymal Transition (EMT) where tumor cells are able to invade vessels, travel to distant tissue, exvade vessels and enter new tissue (E-cadherin, nm-23, CD-44)
 - NB classic syndromes based germline mutations of above genes
 - Li Fraumeni (p53 mutation) = brain, breast, lung, sarcomas
 - Fanconi's Anemia (FA mutation) = leukemia
 - Bloom Syndrome (BLM mutation) = leukemia, lymphoma
 - Ataxia-Telengectasia (ATM mutation) = lymphoma, brain, breast, stomach, ovary
 - Xeroderma Pigmentosa (XP mutation) = skin cancer, leukemia
 - Von Hippel Lindau (VHL mutation)
 - Multiple Endocrine Tumors (MEN-I/RET mutation)
 - Neurofibromatosis Syndrome (NF) = schwannomas, GIST, sarcomas, gliomas, etc
- Types
 - Ectoderm** (skin/nervous system) = squamous carcinomas & neuroendocrine tumor w/ mets thru lymph
 - Skin
 - Nervous System (+neuron specific enolase, chromagranin, synaptogranin, etc)
 - Endoderm** (epithelial lining of gut/airway and glands like liver, pancreas, etc) = adenoma/adenocarcinoma w/ mets thru lymph
 - Most Common Cancer in Adults (exposure of epithelia to environmental carcinogens): 1st: Lung, 2nd: Breast/Prostate, 3rd: Colon
 - GU
 - GI/CEA/CDX1,CK7,CK20/CT
 - breast/CA-15-3/ER,PR,GCDFF/mammogram
 - lung/?/TTF1,CK7/CT
 - prostate/PSA/PSAP/CT
 - pancreas/CA19-9/?/CT
 - ovary/CA-125/CA-125/CT
 - Mesoderm** (everything else including fat, muscle, bone, connective tissue, BM, all vessels) = sarcomas, L&L, germ cell w/ mets thru blood
 - Most Common Cancer in Children (intrinsic genetic factors): 1st: Leukemia, 2nd: CNS, 3rd: Lymphoma, 4th: Sarcoma
 - germ cell/AFP,hCG/PLAP,iso chrom 12p/US
 - lymphoma/LDH/?/BMBx, PET
 - sarcoma/?/c-KIT,actin,desmin,vimentin/CT
 - Teratoma** (≥1 cell type)
 - Not Otherwise Specified (NOS)** don't know the type yet vs **Metastatic Cancer of Unknown Primary (MCUP)** primary site cannot be determined despite extensive diagnostic testing, prognosis is poor b/c CUPs are general poorly responsive to chemo w/ median survival of 3mo, even after post-mortem examination 20% of CUPs still have no primary site, check for pancreatic cancer

Cancer Complications

- Chemo SEs
- Pancytopenia
 - neoplastic blasts accumulate in the BM and suppress hematopoiesis of normal cells resulting in pancytopenia (anemia, thrombocytopenia, and not necessarily leukocytopenia b/c remember the cancer is still there)
- Neutropenic Fever (>101)
 - Remember that other causes of F include tumor itself, meds, transfusions, etc (FUO) but assume it is from infection
 - b/c neutropenia presentation could be subtle i.e. abscess w/o pus, pneumonia w/o infiltrates, cellulitis w/o erythema, etc
 - Neutropenic Precautions
 - ANC <1500 (mild) <1000 (mod) <500 (severe) (at Baylor 500 = 0.50 hence . = ,) WBC x (%Segs + Bands) eg WBC 1.8 Segs 43 Bands 16 = 1800 (0.43+0.16) = 1062
 - Prophylaxis: Levaquin 500mg PO Qd + Fluconazole ? + Famvir 250mg PO BID if + HSV IgG
 - Empiric Tx: (1) Low Risk (not sick, nl labs/studies, nl PEx, no comorbidities, et al) then PO Cipro + Augmentin + Fluconazole vs High Risk (any of the above) IV 4thCeph or Carbapenem or 4thPen/Amino + Fluconazole and add Vanc if hypoTN, catheter, h/o quinolone prophylaxis (2) if no improvement then change antifungal (posiconazole or voriconazole) (3) if no improvement then change antibiotic (Zyvox & Merrem) and anti-fungal (micafungin) (4) if no improvement then call ID and consider drug fever at this point, NB rotate abx thru different lines

- Mechanism: chemo = mucositis = GI flora bacteremia
 - Other: only 30% of time is pathogen identified, more common in liquid vs solid tumors (why? think about it, in liquid tumors immune cells are already affected), prior to abx 75% die
 - Pathogen: Past (Pseudomonas – historically the most common pathogen, E.coli, Klebsiella) vs Now (other GNR and GPC becoming more common now) NB after long standing abx use fungal superinfection develop
 - Labs: CBC, LFTs, UA, HSV serology, EBV/CMV PCR, Influenza nasal swab, TB stuff, fungal studies
 - Cx: panCx (bld x2, sputum, urine, bld fungal) and repeat next day even if persistent fevers (always draw blood from central line and peripheral line)
 - Imaging: esp CXR, CT Head for sinuses, CT Chest
 - PEx: skin (rashes, breakdown, shingles), OP (anything), lung, line sites, surgical sites, perirectal abscess but don't do a DRE
 - Fungal: Candida, Aspergillus, Fusarium vs Viral: HSV, VZV, EBV, CMV, Adeno, Influenza vs Atypical: TB
 - Duration: cont for 2wks if bacteremia or if not sure of source then cont until AF and no longer neutropenic
 - Neutropenic Precautions w/ mask
 - **Typhilitis!!!**
- Spinal Cord Compression
 - Mech: mets (lung, breast/prostate, NHL, RCC, MM) to vertebral body (70% thoracic, 20% lumbar, 10% cervical) extend and cause epidural spinal cord compression
 - S/S: back pain (which may proceed neuro Sx for days), weakness, sensory loss, autonomic dysfxn (overflow incontinence, decreased anal sphincter tone) NB have high index of suspicion b/c so dangerous
 - Dx: STAT whole spine MRI
 - Tx: steroids (Dexamethasone 10mg bolus then 4mg IV Q6hrs) and once +MRI call NS ASAP for emergent surgical decompression for solid tumors and XRT for liquid tumors
- Hyperviscosity Syndrome aka Leukostasis
 - seen primarily in AML (b/c cells are very sticky) when blast >100,000 resulting in occlusion of microvasculature of organs: CNS (TIA/CVA, blurred vision, HA, AMS, retinopathy including vascular engorgement, exudates, hemorrhage), lungs (respiratory distress, hypoxia), penis (priapism), etc
 - Tx: leukopheresis, oxygen, immediate cytotoxic agents, hydrae
- Tumor Lysis Syndrome (TLS)
 - Mechanism: large tumor burden or rapidly proliferating necrotic tumor resulting in **spontaneous** or **chemo induced** (during first few days) release of intracellular contents: high K, high UA, high PO4 and subsequent low Ca, RF 2/2 uric acid stones, high LDH
 - Cancers: aggressive lymphomas (Burkitt's), aggressive leukemias (ALL, AML, blast crisis CML) NB rare for solid tumors
 - Proph: aggressive hydration w/ bicarb, lasix to prevent fluid overload, allopurinol 300 BID or rasburicase 0.15 mg/kg/d
 - Tx: same + treat hyperK, hyperPO4, hypoCa, possible dialysis, consider hydrae
- Bone Mets (refer to Calcium tumor notes)
 - S/S: pain of large bones that have BM esp pelvis, vertebra, sternum, ribs, femur
 - Dx: plain film skeletal survey for lytic vs bone scan for blastic
 - Tx: XRT, bisphosphonates if lytic, vertebroplasty, surgery
- Lung/Liver Mets
 - Tx: surgical resection if well controlled systemic dz or just XRT
- Brain Mets (refer to CNS tumor notes)
- Malignant Effusion
- Paraneoplastic Syndromes: Hypercalcemia of Malignancy, LES, Hypertrophic Osteoarthropathy, SIADH, Cushing, Dermatomyositis
- SVC Syndrome

Leukemia

- clonal expansion of blood cells
- Chronic Leukemias: slow proliferation (therefore can't easily kill with chemo but since slow pts live for awhile ~5yrs) but significant differentiation therefore "mature cell cancer"
- Acute Leukemias: presents acutely over a few weeks rapid proliferation (therefore can easily kill cancer cells but must do so quickly) but limited differentiation therefore presence of increased blasts (>20% in BM and + in PBS), sometimes there is aleukemic leukemia where there is just pancytopenia and no blasts

Performance Status

- Karnofsky Score (0% Bad - 100% Good) vs ECOG Score (5 Dead - 0 Good)
- even pts w/ identical tumors w/ only different performance status their prognosis is very different

Chemo

- General Principles

- Three Cell Types: actively dividing (few, most chemosensitive), resting cell but capable of dividing (most), resting cell with NO potential for division (some, not chemosensitive)
- Gompertzian Principle (the larger the tumor the fewer actively dividing cells)
- G1 (protein synthesis for S) S (DNA repair/synthesis) G2 (protein synthesis for M) M (Mitosis) vs G0 (nondividing but capable)
- the mechanism of many of these drugs is multiple and the mechanism taught in medical school is likely NOT the primary mechanism
- Phases of Chemo
 - 1st **Induction**: goal is to reduce counts to below the level that current technology is able to detect cancer cells, however, cancer cells still exist so-called "minimal residual disease" (MRD) hence "consolidation" therapy
 - 2nd **Consolidation**: additional chemo or even autologous/allogenic BM transplant is necessary for complete eradication of cancer esp in CSF which must be tapped during remission b/c it can be a sanctuary for occult disease
 - 3rd **Maintenance**: longest phase of chemotherapy
- Partial Remission (identifiable but less cancer)
- Complete Remission (no more identifiable cancer)
- Cure (CR over a specific period of time depending on the cancer)
- Glucocorticoids
- Cytotoxic (cause the classic chemo SEs of alopecia, N/V, hematopoietic suppression)
 - **Alkylators** (alkylate guanine causing cross-linking, strand breaking, prevention of uncoiling, etc most active cell arresting chemo, high doses used for chemo vs low doses used for immunosuppression by inhibiting T/B cell production, SEs: **myelosuppression, leukemogenic, N/V, alopecia, sterility, menstrual abnormalities**)
 - **Oxazaphosphorines**: cyclophosphamide (Cytosan), ifosfamide (Ifex), melphalan (Alkeran), chlorambucil (Leukeran) SEs: **hemorrhagic cystitis, bladder malignancy, chronic bladder fibrosis** 2/2 the toxic metabolite acrolein bathing the bladder wall (can be mitigated with mesna which binds acrolein), SIADH, renal tubular damage, neurotoxicity, acute cardiac necrosis
 - **Platinums**: cisplatin (Platinol), carboplatin (Paraplatin), oxaliplatin (Eloxatin) SEs: **ototoxicity, peripheral neuropathy, nephrotoxicity, AIHA, allergic rxn**
 - **Alkylsulfonates**: busulfan (Myleran) SEs: chronic pulmonary fibrosis, wasting syndrome that is like Addison's disease but w/o decreased cortisol, cataracts, glossitis/cheilosis, neurotoxicity, hepatic VOD
 - **Hydrazines/Triazines**: procarbazine (Matulane), altretamine (Hexalen), temozolomide (Temodar) SEs: neurotoxicity/neuropathy, serotonin syndrome as these agents are MAOIs, disulfiram like rxn, allergic rxn,
 - **Nitrosureas**: lomustine (CeeNU), dacarbazine (DTIC-Dome), mitomycin (Mutamycin) SEs: **HUS/TTP**, interstitial pneumonitis w/ fibrosis, anorexia, nephrotoxicity, hepatic VOD, skin damage from extravasation, flu-like syndrome
 - **Plant Alkyloids**
 - **Anti-Microtubule Vincas** (from Periwinkle Plant): vincristine (Vincristine), vinblastine (Vinblastine), vinorelbine (Navelbine) SEs: myelosuppression, N/V, b/c they affect microtubules and b/c axon fxn relies on microtubules then **peripheral neuropathy**, cellulitis/phlebitis 2/2 soft tissue drug extravasation, myalgias, D/C, alopecia, stomatitis
 - **Anti-Microtubule Taxoids** (from Pacific Yew Tree): paclitaxel (Taxol), docetaxel (Taxotere), IV, SEs: myelosuppression, allergic rxn (so common that you pre-Tx w/ steroids and histamine blockers and slowly infusion), flu-like syndrome, alopecia, mucositis, neuropathy like the vincas
 - **Topoisomerase Inhibitor Podophyllotoxins** (from May Apple Plant): etoposide (VP-16) IV/PO, SEs: myelosuppression, N/V, D, alopecia, flu-like syndrome, allergic rxn, MOST LEUKOMOGENIC OF ALL CHEMOTHERAPY
 - **Topoisomerase Inhibitor Camptothecins** (from Asian Happy Tree): irinotecan (Camptosar), topotecan (Hycamtin) IV, SEs: myelosuppression, N/V, alopecia, D/C, flu-like syndrome, mucositis, SOB/cough, HA, rash
 - **Anti-Metabolites** (similar to metabolites needed for DNA/RNA synthesis and compete for enzymes)
 - **Cytosine Analogues**: cytarabine (AraC) IV, SEs: N/V, myelosuppression peaking 7-14d, mild alopecia/stomatitis/D, rare pulmonary edema, typhilitis syndrome, pancreatitis, neurotoxicity
 - **Adenosine Analogues**: cladribine (Leustatin) IV, SEs: myelosuppression, rash, fludarabine (Fludara) SEs: myelosuppression, N, D, neurotoxicity, interstitial pneumonitis pentostatin (Nipent) SE: myelosuppression, neurotoxicity, anorexia, conjunctivitis, serositis
 - **Pyrimidine ("PCT") Analogues**: 5-Fluorouracil (5-FU Adrucil) IV, Capecitabine (Xeloda) PO, Gemcitabine (Gemzar) PO NB leucovorin potentiates its effect, SEs: **mucositis, cerebellar ataxia**, N/V, anorexia, enteritis, typhilitis, diarrhea, hand-foot syndrome, tear duct fibrosis, Coumadin-Gemzar interaction (NB leucovorin is a folate acid derivative and is used to rescue after chemo)
 - **Purine ("PUGA") Analogues**: azathioprine (Azasan/Imuran) and 6-Mercaptopurine (6-MP, Purinethol) (refer)
 - **Folic Acid Analogues**: methotrexate (Trexall) (refer)
 - **RNA Reductase**: Hydroxyurea (Hydrea) IV/PO, SEs: marrow suppression, skin changes

- **Antitumor Antibiotics**
 - **Anthracyclines** (generate reactive oxygen radicals that cause DNA strand breaking but many other theories exist and the exact mechanism is likely multifactorial): doxorubicin (Adriamycin), daunorubicin (Cerubidine), epirubicin (Ellence), idarubicin (Idamycin), mitoxantrone (Novantrone)
SEs: **cardiac toxicity** (1) arrhythmia, (2) pericarditis, (3) chronic dilated CM (follow w/ MUGA scan) can be mitigated w/ dexrazoxane which chelates iron in the heart preventing formation of radicals, myelosuppression, mucositis, alopecia, N/V, hyperpigmentation, bladder irritation
 - **Other: bleomycin (Blenoxane)** Mech: intercalates, SEs: **pulmonary fibrosis**, infusion fever, mucocutaneous changes (induration, hyperesthesia, ulceration, hyperpigmentation), alopecia, HUS/TTP, CAD, hypercalcemia, dactinomycin (Cosmegen) Mech: intercalates, SEs: myelosuppression, N/V, alopecia, stomatitis, anorexia, acne, hepatic VOD, plicamycin (Plicamycin) Mech: complexes with guanine, SEs: bleeding diathesis, N/V, D, stomatitis, diarrhea, anorexia
- **Biologics/Targeted**
 - **Anti-CD20:** rituximab (Rituxan), ibritumomab (Zevalin), tositumomab (Bexxar) for B-lymphocyte neoplasms, SEs: infusion rxn (mild pulmonary dysfxn to ARDS and mild cardiac dysfxn to MI/VF/Shock therefore pre-Tx w/ Tylenol/Benadryl), allergic rxn, TLS, arrhythmia
 - **Anti-HER2** (Human Epithelial growth factor Receptor): trastuzumab (Herceptin) for Breast Cancer, erlotinib (Tarceva) for NSCLC, panitumumab (Vectibix) for CRC, SEs: infusion rxn (mild flu-like symptoms), cardiac toxicity
 - **Anti-CD33:** gemtuzumab (Mylotarg) for AML when pt cannot take cytotoxic chemo, SEs: myelosuppression, infusion rxn thus premedicate
 - **Anti-CD52:** alemtuzumab (Campath) for CLL, SEs: VERY SEVERE myelosuppression, infections (PCP/HSV prophylaxis), infusion rxn thus pre-medicate
 - **Anti-EGFR** (Epidermal Growth Factor Receptor): cetuximab (Erbix), trastuzumab (Herceptin), gefitinib (Iressa) for CRC and SCC of Head&Neck, SEs: acne, allergic rxn
 - **Anti-VEGF** (Vascular Endothelial Growth Factor): bevacizumab (Avastin) for CRC, SEs: HTN, intestinal perforation, infusion rxn, wound healing problems, DVT-PE
 - **Farnesyl Transferase Inhibitors** (tipifarnib (Zarnestra)) inhibits mutant K-ras function
 - **Tyrosine Kinase Inhibitors:** imatinib (Gleevec) & dasatinib (Sprycel) for CML, gefitinib (Iressa) for SCLC, sunitinib (Sutent) for RCC/GIST, sorafenib (Nexavar) for RCC SEs: N/V, D, rash
 - **Proteasome Inhibitors** (Mech: proteasomes are complex enzymes found in all cells that are responsible for multiple cell fxns including protein degradation, cell adhesion, cytokine production): bortezomib (Velcade) for MM
 - **IMiDs** (Mech: immunomodulatory agents which affect the immune system in various ways): thalidomide (Thalomid), lenalidomide (Revlimid) for MM
 - **IFN:** Recombinant IFN alpha -2a, -2b, -n3 SEs: depression to psychosis, flu-like symptoms, myelosuppression, rash