Chemotherapy
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MSU SCS Board Review Course

Normal Cell Growth

- Static
  - Well-differentiated cells that rarely undergo division after initial proliferation
- Expanding
  - Cells that have capacity to proliferate under special stimuli (injury)
- Renewing
  - Constantly in proliferative state

Cancer Cell Growth

- Gompertzian growth
  - When tumors are small they follow an exponential pattern and then slow down
  - As a tumor mass increases in size the time required to double the tumor volume also increases
Cell Cycle

- Generation time is from M-phase to M-phase
- M phase (mitosis)
  - Cell division
- G1 phase (post mitotic phase)
  - Protein and DNA synthesis continue. Cells can differentiate or continue in proliferative phase
- S phase (DNA synthesis)
  - DNA replication occurs
- G2 phase (post synthesis)
  - Cell has diploid number of chromosomes and twice the DNA content. Cell remains here for short time and enters mitotic phase again
- G0 phase (resting phase)
  - Cells do not divide. Cells can move in and out of G0 phase

Cell cycle and chemotherapy

- Dividing cells in the cell cycle are very sensitive to chemotherapy
- Cells in the resting phase are insensitive to chemotherapy

Cell cycle specific Chemotherapy

- G1
  - Actinomycin D
- Early S
  - 5-Fluorouracil, Methotrexate
- Late S
  - Doxorubicin
- G2
  - Bleomycin, Etoposide, Carboplatin, Cisplatin, Topotecan, Radiation
- M
  - Paclitaxel, Vincristine, Vinblastine
Log Kill Hypothesis
- Chemotherapy kills a constant fraction of cells rather than a constant number.

Resistance
- Goldie-Coldman hypothesis (model of spontaneous drug resistance)
- Tumors are curable with chemo if no permanently resistant cells are present and if chemo is begun before resistance develops.
- If only one chemo drug is used, then the probability of cure diminishes rapidly with the development of a single resistant line.
- Minimize emergence of drug resistance requires multiple effective drugs and that they be given early in patients disease.

Limitation of single agent chemotherapy
- Toxicity limits the dose and duration of drug administration and thus restricts the tumor cell kill achievable.
- Adaptive mechanisms allow cell survival and eventual regrowth of resistant tumor cells in spite of lethal effects produced in the bulk of the tumor.
- Drug resistance may spontaneously develop.
- Multidrug or pleiotropic drug resistance may develop.
Combination chemotherapy

- Different chemotherapy drugs act in different phases of the tumor cell cycle
- Multiple drugs with different characteristics reduce the tumor mass more completely than any individual chemo agent while minimizing the impact of a single chemo agent

Combination Chemotherapy

- Drugs must be active as single agents against the tumor
- Different mechanisms of action to minimize emergence of resistance
- Drugs should be additive if not synergistic effect
- Drugs should have different toxicity

Remission

- Complete Remission
  - Complete disappearance of all objective evidence of tumor as well as the resolution of all signs and symptoms referable to the tumor
- Partial Remission
  - 30% - 50% reduction in the size of all measurable lesions along with some degree of subjective improvement and the absence of any new lesions during therapy
Classes of Chemotherapy

- Alkylating Agents
  - Cyclophosphamide, ifosfamide, cisplatin, carboplatin
- Anti-tumor Antibiotics
  - Doxorubicin, liposomal doxorubicin, actinomycin D, bleomycin
- Antimetabolites
  - Methotrexate, 5-fluorouracil, gemcitabine
- Plant Alkaloids
  - Vinblastine, vincristine, paclitaxel, docetaxel, etoposide
- Topoisomerase-I Inhibitors
  - Topotecan
- Anti-angiogenic
  - Bevacizumab

Alkylating Agents

- Bind to key DNA sites
- Interfere with accurate base pairing, cross-linking DNA, and produce single stranded and double stranded DNA breaks
- Inhibit DNA, RNA, protein synthesis
- EX: Cyclophosphamide, ifosfamide

Cyclophosphamide

- Toxicity
  - Alopecia, hemorrhagic cystitis, metallic taste, cardiac necrosis, SIADH, myelosuppression
Ifosfamide

- Excreted in the bladder so renal insufficient patients at increased risk of toxicity
- Toxicity
  - Alopecia, myelosuppression, facial flushing
  - Hemorrhagic cystitis
  - CNS syndrome

Hemorrhagic cystitis

- The active metabolite can breakdown to form Acrolein which is a bladder irritant
- Acrolein will bind nonspecifically to the bladder epithelium
- Treat with MESNA (N-Acetylcystein, sodium, 2-mercaptopoethane sulfonate) and adequate hydration

CNS Syndrome

- Somnolence, lethargy, ataxia, confusion, disorientation, dizzy, malaise, coma
- Caused by chloroacetaldehyde metabolism
- Treatment is methylene blue
Alkylating-like compounds

- Carboplatin
- Cisplatin

MOA
- Platinum containing compound that forms adducts with DNA.
- Distorts the DNA by bending helix up to 40 degrees
- Inhibits DNA synthesis

Carboplatin
- Treated by AUC (area under the curve dosing) based on creatinine clearance
- Toxicity
  - Myelosuppression (thrombocytopenia), peripheral neuropathy, nephrotoxicity, secondary leukemia
  - Hypersensitivity reaction (itching, erythema, tachycardia, wheezy, chills, hypotension)
  - Treat with steroids and Benadryl

Cisplatin
- Toxicity
  - Myelosuppression, nausea / emesis
  - Peripheral neuropathy
  - Ototoxicity (high frequency hearing loss)
  - Nephrotoxicity
Anti-tumor Antibiotics
- Isolated as a natural product from fungi in the soil
- Interact with drug and DNA called intercalation (drug inserts between DNA base pairs)
- Form free radicals capable of damaging DNA, RNA and proteins
- Ex: Anthracyclines (doxorubicin, liposomal doxorubicin)
- Actinomycin D, Bleomycin, Mitomycin C

Doxorubicin (adriamycin)
- From Streptomyces peucetius varicaeius
- Toxicity
  - Leukopenia, Thrombocytopenia, Mucositis, Stomatitis
  - Cardiomyopathy
- Cardiomyopathy causes CHF
  - Max lifetime dose 450 mg/m2
  - Cardiomyopathy based on dose
    - 31% = 450 mg/m2
    - 7% = 550 mg/m2
    - 15% = 600 mg/m2
    - 40% = 700 mg/m2

Liposomal doxorubicin HCL (Doxil)
- Doxorubicin encapsulated in a liposome
- Toxicity
  - Myelosuppression
  - Stomatitis
  - Palmar-plantar erythrodysesthesis (Hand & Foot Syndrome)
    - Painful erythema and edema
  - Acute infusion reaction
    - Flushing, chill, back pain, SOB, hypotension
  - Cardiomyopathy
    - Less common than doxorubicin
Actinomycin D

- Streptomyces parvulus
- Toxicity
  - Myelosuppression, nausea / emesis
  - Erythema, hyperpigmentation
  - Delayed radiation recall skin damage
  - Interact with radiation therapy

Bleomycin

- Streptomyces Verticillus
- Toxicity
  - Myelosuppression, hyperpigmentation
  - Pulmonary Fibrosis
  - Pulmonary toxicity
  - Dependent on increased cumulative lifetime dose of >400 mg

Antimetabolites

- Resemble analogues of normal purines and pyrimidines
- Disrupts functions crucial to viability of cell
- Examples
  - Methotrexate
  - 5-fluorouracil
  - Gemcitabine
Methotrexate
- Inhibition of dihydrofolate reductase that leads to depletion of intracellular tetrahydrofolate pool
- Deplete folate
- Arrest of DNA, RNA, protein synthesis
- Toxicity
  - Myelosuppression, Alopecia, mucositis, increase LFT's, pneumonitis, Nephrotoxicity (watch in patient with renal insufficiency)
  - Rescue with leucovorin (folinic acid)

5- Fluorouracil
- Inhibits thymidylate synthase leads to inhibit of DNA synthesis through depleted thymidine
- Treatment of ovarian, cervical cancer
- Toxicity
  - Myelosuppression
  - Watery diarrhea, Stomatitis, Mucositis
  - Increase LFTs, Photosensitivity
  - Cerebellar syndrome (Headache, ataxia, nystagmus, confusion) (secondary to metabolite fluorocitrate)
  - Keratitis

Gemcitabine
- Inhibit of ribonucleotide reductase blocks conversion of ribonucleotides to deoxyribonucleotides thus blocking DNA synthesis
- Inhibits DNA polymerase
- Toxicity
  - Myelosuppression, Stomatitis
  - Radiation recall, Hemolytic uremic syndrome
  - Somnolence, increase bilirubin and alk. Phosphatase
  - Hematuria, proteinuria
Plant Alkaloids

- Derived from a plant
- Disturbance of normal assembly, disassembly and stabilization of intracellular microtubules
- Vincristine / Vinblastine
- Paclitaxel
- Etoposide

Vincristine / Vinblastine

- From the periwinkle plant
  - Catharanthus roseus
- Structurally the same except presence of a methyl group (vinblastine) or formyl group (vincristine)
- Causes mitotic arrest by inhibiting mitotic spindle formation
- Inhibits microtubule assembly
- Toxicity
  - Myelosuppression, Alopecia, peripheral neuropathy, Bronchospasm, anaphylactic reaction
  - Obstipation, photosensitivity – Vinblastine
  - Cortical blindness, increased SGOT:SGPT – Vincristine

Paclitaxel (taxol)

- Western yew tree
  - Taxus brevifolia
- Promotes assembly of microtubules and stabilizes them preventing depolymerization
- Inability to depolymerize prevents cellular replication
- Toxicity
  - Neutropenia, Alopecia
  - Hypersensitivity reaction (flushing, hypotension, urticaria)
  - Peripheral neuropathy, Fatigue
**Docetaxel (Taxotere)**
- European yew tree
- *Taxus baccata*
- Promotes microtubule assembly and inhibits depolymerization of tubulin
- Halts cell division in M phase and prevents replication
- Toxicity
  - Neutropenia, hypersensitivity, alopecia, mucositis
  - Neuropathy = less than paclitaxel

**Etoposide**
- Mandrake plant
- *Podophyllum peltatum*
- Binds microtubular subunit tubulin and inhibits microtubule assembly
- Inhibits topoisomerase II enzyme causing DNA stand breaks
- Toxicity
  - Leukopenia, nausea / emesis, alopecia, HTN, Neuropathy, Fatigue, Vertigo, Anorexia

**Topoisomerase I inhibitors**
- Inhibit enzyme topoisomerase-1
- Important enzyme in DNA replication, repair and transcription
- Bind to the enzyme-DNA complex leading to permanent stand break and cell death
- Ex.
  - Topotecan
Topotecan

- Wood stem of Chinese tree
- Camptotheca acuminata

Toxicity
- Myelosuppression
- Nausea / emesis
- Diarrhea, mucositis, alopecia

Anti-angiogenic

- Effects on normal and abnormal blood vessels delivering nutrients to the malignancy
- Ex
  - Bevacizumab

Bevacizumab (Avastin)

- Recombinant humanized monoclonal IgG1 AB designed to inhibit angiogenesis through targeting VEGF
- Toxicity
  - Hypertension, Diarrhea, Leukopenia
  - GI perforation, Hemorrhage
  - (increased HTN, proteinuria, CHF with use)