Cancer Chemotherapy

❋ This lecture is mainly conceptual; therefore, I advise you to study its sheet (sheet 6) and merely revise from this summary

Modalities of Cancer Chemotherapy		
Curative	**Palliative**	**Adjuvant**
-Only in 10-15% of cases -In certain disseminated neoplasms	Given only to relieve the symptoms temporarily and enhance the overall quality of life, not to cure the cancer	Given as an adjuvant to surgery, even if there is no evidence of metastasis

Ideal Anticancer Drugs	Current Anticancer Drugs
-Exploits the differences between normal & tumor cells. -Broad spectrum of activity -Good distribution through the body -Non-immunogenic -Adequate biological half-life -Reasonably priced	-Carcinogenic -Mutagenic -Teratogenic -Immunosuppressive -Very toxic, but tolerance can develop

Gompertzian Tumor Growth	-The growth rate of a tumor is not constant and peaks when the tumor is about one third of its maximum size -Gompertzian growth curve describes the complex pattern of tumor growth. The curve has an early, almost exponential growth rate followed by slower growth rate which reaches a plateau as tumors grow larger in size.
Log-Kill Hypothesis (Exponential Cell Kinetics)	-Drugs can kill tumor cells by Exponential Cell Kinetics mechanism called Log-Kill Hypothesis -(In acute leukemias and aggressive lymphomas) If the drug efficacy is 99.99%, and the number of cells at the time of diagnosis was 10^{12}, this drug will kill 10^{4} cells → 10^{8} cells are in remission (in addition to cells that are inherently resistant, cells not available to the drug (CNS, teste) and cells in G0 phase → more than 10^{8} in remission.

Cancer Chemotherapy		
Combination Chemotherapy	**Toxicity**	**Special Problems**
-Anticancer drugs are usually given in combinations to: **Increase** effectiveness & **Reduce** the toxicity -Employed to **overcome** the limited log kill of individual drugs -The drugs should be **effective** when used as **single** agents - If there is no biochemical basis for synergism, there should be at least **additive effects** -Where possible, drugs with **differing modes of actions** are combined (Myelosuppressant & nonsuppressant) -The major toxicity of each drug, should be as different as possible from that of other agents (**nonoverlapping toxicity**) -Toxicity appears at different times	-Cytotoxic drugs are given in repeated courses arranged so that the recovery of normal cells can occur, but little recovery of cancer cells is possible - "**Magic bullet**" drug, is a dream that hasn't been materialized yet -Cells of the bone marrow, the lymphatic system, and the lining of the intestinal tract are very sensitive to cytotoxic drug effects -Almost all anticancer drugs cause toxicity: ***Bone marrow suppression:** Nitrogen mustard. ***Immunosuppression**: Methotrexate ***Neuropathy**: Vincristine ***Cardiotoxicity**: Doxorybicin (Adriamycin)	-Need special storage strategies -Preparation -Administration techniques -Extravasation of injection: (IV administration causes vasculitis and irritation of blood vessels) -Oral administration results in vomiting - so we combine them with other drugs to decrease this effect, like: ***Lorazepam** (for *anxiety*) ***Dexamethasone, Domperidone** ***Ondansetron -5HT3 antagonist-** (for *vomiting*) -Teratogenesis. -Bone Marrow suppression. -Immunosuppression leading to severe infections

Relative Chemosensitivity of Tumors			
Highly Sensitive	**Moderately Sensitive**	**Relatively Insensitive**	**Resistant Tumors**
May be cured by chemotherapy	chemotherapy may sometimes contribute to cure and often palliates	Chemotherapy may sometimes produce palliation	(Melanoma, squamous cell carcinoma of the lung, large bowel cancer)

Cell Cycle	
G0	Resting phase (Cancer cells in the G0 are least sensitive to chemotherapy)
G1	Initial phase, enzyme synthesis
S	DNA synthesis
G2	Synthesis of cellular components required for mitosis
M	Mitosis, Cell division phase

Resistance to Cytotoxic Drugs			
Primary or Inherent Resistance	**Acquired Resistance**		
	Highly Specific	**Multidrug-Resistance (Pleiotropic)**	**Biochemical Resistance**
Absence of response on the first exposure, and they should not be treated with chemotherapy. (e.g.: - Melanoma, renal cell carcinoma, brain cancer)	-For one single drug -Based on a change in the genetic apparatus of a given tumor cell with amplification or increased expression (gene amplification) of one or more specific genes	-Resistance to a variety of natural product anticancer agents of different structures developing after exposure to a single agent. -Associated with increased expression of a normal gene (the MDR1gene) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux -This glycoprotein requires ATP to expel a variety of foreign molecules and not limited to anticancer drugs. -Reversed by calcium channel blockers -Could also be due to overexpression of the multidrug resistance protein1 (MRP1) which can function as a drug export pump	-Decreased drug transport into the cells. Alteration in the structure of the target enzyme -Changes in cell DNA repair capability

Cell-Cycle-Specific Drugs (CCS)	Cell-Cycle-Nonspecific Drugs (CCNS)
- Exert their action on cells traversing the cell cycle. -Effective only when large proportion of the cells are proliferating or are in the growth fraction. -**Examples**: Antimetabolites, Antitumor Antibiotics, Epipodophyllotoxins, Taxanes, Vinca Alkaloid	-Can sterilize tumor cells whether they are cycling or resting or resting in the G0 compartment -They can kill cancer cells even if they are slowly multiplying -Useful both in low growth fraction solid tumors as well as in high growth fraction tumors -Bind to cellular DNA and damage these macromolecules -**Examples**: Alkylating Agents, Anthracycline, Antitumor Antibiotics, Camptothecins, Platinum Compounds

Complications of Chemotherapy	
Immediate Complications	**Long-term Complications**
-Nausea and vomiting -Mucosal ulcerations -Bone marrow depression -Alopecia	-Infertility -Secondary cancers -Pulmonary fibrosis -Cardiomyopathy -Nerve damage -Loss of hearing -Renal impairment

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