Cancer Chemotherapy

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Modalities of Cancer Chemotherapy

**Curative:**
Only in 10-15% of cases.

In certain disseminated neoplasms. Solid tumors are more difficult to eradicate compared to solid cancers. Example: leukemia has a greater chance of spread than solid cancers.

**Palliative:**
Given only to relieve the symptoms temporarily and enhance the overall quality of life, not to cure the cancer.

**Adjuvant:**
Given as an *adjuvant* to surgery, even if there is no evidence of metastasis. Chemotherapy rarely eradicates escaping cells to prevent their spread in the body. Cure mainly depends on excision of tumor.

Chemotherapy is rarely curative, mostly palliative or adjuvant.
Cancer Chemotherapy

• Classes of Anticancer Drugs:
  • Signal Transduction Inhibitors.
  • Microtubule Inhibitors.
  • Differentiation agents.
  • Antimetastatic Drugs.
  • Antiangiogenic drugs. → anti- blood vessel formation, cuts its nutrition (patho)
  • Hypoxic Tumor Stem Cell- specific.
  • Tumor Radiosensitizing.
  • Normal Tissue Radioprotecting Drugs. → protects surrounding tissue
  • Cytoprotective Agents.
  • Biologic Response Modifiers. → enhance immunologic response of patient

there is no ideal anti-cancer drug.
Current Anticancer Drugs

- Carcinogenic.
- Mutagenic. \( \rightarrow \) causes mutations.
- Teratogenic. \( \rightarrow \) congenital abnormality in pregnant women.
- Immunosuppressive.
- Very toxic but tolerance develops.

late side effect: although they treat cancer, they can cause other cancers in other organs

nausea & diarrhea occur in 100% of patients
The Ideal Anticancer Drugs

• Exploits the differences between normal and tumor cells.
• Broad spectrum of activity.
• Good distribution through the body.
• Non-immugenic. → not induce allergic rxns unlike antimicrobials
• Adequate biological half life. → can use drug infrequently.
• Reasonably priced. → there are anticancers that are very expensive.
this graph is true for leukemia

treatment after tumor reached maximum size → low curative rate

gradual, flattening of growth.

patient starts feeling symptoms.

size of tumor grows exponentially in a short period of time → difficult to discover in early stage
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.
Fig. 7. Norton-Simon relationship between tumor size (A), instantaneous growth fraction (GF) (B), and growth rate (C) for unperturbed Gompertzian growth. While the GF is maximum at the time of initiation of growth the growth rate is maximum when the tumor is about 37 percent of its limiting size.\(^5\) (Reproduced from Cancer Treat Rep.\(^{13}\))
Log-Kill Hypothesis
(Exponential Cell Kinetics)

In acute leukemias and aggressive lymphomas:

- Cells at time of diagnosis: $10^{12}$.
- A very effective drug can kill 99.99%.
- So, cells in remission: $10^8$. (remaining cells)
- Also add, the number of cells that are inherently resistant, cells not available for the drug (CNS, testes), and cells in the $G_0$ phase.

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LOG kill hypothesis

- The example shows the effects of tumor burden, scheduling, initiation/duration of treatment on patient survival.
- The tumor burden in an untreated patient would progress along the path described by the RED LINE –
- The tumor is detected (using conventional techniques) when the tumor burden reaches $10^9$ cells
- The patient is symptomatic at $10^{10}$-$10^{11}$ cells
- Dies at $10^{12}$ cells.

If tumor can’t be removed surgically → chemotherapy & anti-cancers.
Combination Therapy

- 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.
  \[ 1 + 1 = 2 \]
  \[ 1 + 1 > 2 \]
- Where possible, drugs with differing modes of actions are combined.
  Synergism usually occurs when drugs work on different mechanisms.
Combination Chemotherapy

• The major toxicity of each drug, should be as different as possible from that of other agents (non overlapping toxicity).
• Toxicity appears at different times.
• Myelosuppressant & nonsuppressant.
Cancer Chemotherapy

• “Magic bullet” drug, is a dream that did not materialize yet.
• 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.

normal cells are also damaged
but their recovery is faster
than cancer cells
Toxicity of Cancer Chemotherapy

- 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, e.g.:
  - Bone marrow suppression: Nitrogen mustard.
  - Immunosuppression: Methotrexate.
  - Neuropathy: Vincristine.
  - Cardiotoxicity: Doxorybicin (Adriamycin).
Special Problems/Practical Points

- **Storage**: → they need special environment for storage.
- **Preparation**.
- **Administration**: → IV/oral
  - there are special instructions that should be followed.
- **Extravasation of injection**.
- **Vomiting**:
  - Lorazepam for anxiety. (anti-anxiety drug before treatment)
  - Dexamethasone, Domperidone.
  - Ondansetron: 5HT_3_ antagonist.
- **Teratogenesis**: → can affect fetus causing congenital anomalies. (risk: benefit ratio considered)
- **Bone Marrow suppression**.
- **Immunosuppression leading to severe infection**: → isolation of cancer patient.
Relative Chemosensitivity of Tumors

- **Highly Sensitive:** high chances of cure.
- *May be cured by chemotherapy.*
  - Teratoma of Testis.
  - Hodgkin’s and high grade non-Hodgkin’s Lymphomas. (recall patho, 100% curative)
  - Wilm’s Tumor.
  - Embryonal Rhabdomyosarcoma.
  - Choriocarcinoma. early phases of pregnancy (placenta) 100% curable
  - Acute Lymphoblastic Leukemia in children.
  - Ewing’s Sarcoma.
Relative Chemosensitivity of Tumors

• Moderately Sensitive:
  • *Chemotherapy may sometimes contribute to cure and often palliates.*
    • Small cell carcinoma of the lung.
    • Breast carcinoma.
    • Low grade non Hodgkin’s Lymphoma.
    • Acute Myeloid Leukemia.
    • Ovarian cancer.
    • Myeloma.
Relative Chemosensitivity of Tumors

- **Relatively Insensitive:** 
  - Chemotherapy may sometimes produce palliation.
  - Reduce size of tumor (palliative care)
  - Gastric carcinoma.
  - Bladder carcinoma.
  - Squamous cell carcinoma of head and neck.
  - Soft tissue sarcoma.
  - Cervical carcinoma.
Relative Chemosensitivity of Tumors

- **Resistant Tumors:**
  - Melanoma.
  - Squamous cell carcinoma of the lung.
  - Large bowel cancer.
Resistance to Cytotoxic Drugs

**Primary or Inherent Resistance:**
Absence of response on the first exposure.
• Like melanoma, renal cell carcinoma, brain cancer.

**Acquired Resistance:**
1. **Highly Specific:**
• 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.
2. **Multidrug-Resistance (Pleiotropic):**

- 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 *MDR1* gene) for a cell surface glycoprotein (P-glycoprotein) involved in drug efflux.
2. **Multidrug-Resistance (Pleiotropic): cont...**

- 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.

*Pumps drug out the cell*
Resistance to Cytotoxic Drugs

3. **Biochemical Resistance:**
   Decreased drug transport into the cells.
   Alteration in the structure of the target enzyme.
   Changes in cell DNA repair capability.
Complications of Chemotherapy

• **Immediate Complications:**
  • Nausea and vomiting.
  • Mucosal ulcerations.
  • Bone marrow depression.
  • Alopecia.
Complications of Chemotherapy

- **Long term complications:**
  - Infertility.
  - Secondary cancers.
  - Pulmonary fibrosis.
  - Cardiomyopathy.
  - Nerve damage.
  - Loss of hearing.
  - Renal impairment.
Cancer Chemotherapy

• Cells, normal and cancerous, pass through a series of phases during its life.
• Cancer cells in the $G_0$ will be in the resting phase, and they will be least sensitive to chemotherapy.
• Cytotoxic drugs interfere with DNA or RNA and thus have profound effects on cells, normal and malignant.
Cell Cycle

• **G₀**: Resting phase.

• **G₁**: Initial phase, enzyme synthesis.

• **S**: DNA synthesis.

• **G₂**: Synthesis of cellular components required for mitosis.

• **M**: Mitosis, Cell division phase.
**Cell Cycle Phases**

**S phase**
DNA is replicated.

**G_1 phase**
Cell metabolically active; duplicates organelles and cytosolic components; starts replicating centrosomes.

**G_2 phase**
Cell growth continues; enzymes and other proteins are synthesized and replication of centrosomes is completed.

**G_0**
(Exit from cell cycle-nondividing cell)

**Interphase**
- 6-8 hours
- 8-10 hours
- 4-6 hours

**Mitotic (M) phase**
The Cell Cycle and Anticancer Drugs

Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle–specific (CCS) drugs.

A second group of agents called cell cycle–nonspecific (CCNS) drugs can kill tumor cells whether they are cycling or resting in the $G_0$ compartment. CCNS drugs can kill both $G_0$ and cycling cells (although cycling cells are more sensitive).
Cell-Cycle-Specific Drugs (CCS)

• 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.
Cell-Cycle-Specific Drugs (CCS)

- **Antimetabolites:**
  - Capecitabine.
  - Cladribine.
  - Cytarabine.
  - Fludarabine.
  - 5-Fluorouracil (5-FU).
  - Gemcitabine.
  - 6-Mercaptopurine (6-MP).
  - Methotrexate.
  - 6-Thioguanine (6-TG).

Throughout the next couple of slide, just know the main classes of drugs, the names the Doctor wants us to know will be focused on in the next lecture, DON'T TRY MEMORIZING THEM
Cell-Cycle-Specific Drugs (CCS)

• **Antitumor Antibiotics:**
  - Bleomycin.

• **Epipodophyllotoxins:**
  - Etoposide.
  - Teniposide.
Cell-Cycle-Specific Drugs (CCS)

- **Taxanes:**
  - Docetaxil.
  - Paclitaxil.

- **Vinca Alkaloids:**
  - Vinblastine.
  - Vincristine.
  - Venorelbin.
Cell-Cycle-Nonspecific Drugs (CCNS)

• Can sterilize tumor cells whether they are cycling or resting or resting in the G₀ compartment.

• Useful both in low growth fraction solid tumors as well as in high growth fraction tumors.

• Bind to cellular DNA and damage these macromolecules.
Cell-Cycle-Nonspecific Drugs (CCNS)

- **Alkylating Agents:**
  - Busulfan.
  - Carmustine.
  - Cyclophosphamide.
  - Lomustine.
  - Mechlorethamine.
  - Melphalan.
  - Thiotepa.

- ** Anthracyclines:**
  - Daunorubicin.
  - Doxorubicin.
  - Epirubicin.
  - Idarubicin.
  - Mitoxantrone.
Cell-Cycle-Nonspecific Drugs (CCNS)

• **Antitumor Antibiotics:**
  - Dactinomycin.
  - Mitomycin.

• **Camptothecins:**
  - Irinotecan.
  - Topotecan.

• **Platinum Compounds:**
  - Carboplatin.
  - Cisplatin.
  - Oxaliplatin.