Anti-Cancer Drugs

- By
- GL Muntingh
- Dept of Pharmacology

Cancer

- It is basically a disease of cells characterized by the shift in the control mechanism that govern cell proliferation and differentiation.

Special Characteristics of Cancer Cells

- Uncontrolled Proliferation
- Dedifferentiation and loss of function
- Invasiveness (Spreading)
- Metastasis (spread of cancer from its primary site to other places in the body)

Management of Cancer

- Surgical
- Radiation
- Chemotherapy

- The neoplastic cell burden is initially reduced either by surgery and /or radiation followed by chemotherapy or combination therapy.

Chemotherapy

Types of Therapies:

- **Adjuvant:** Additional treatment after the primary treatment to lower the risk that the cancer will come back.
- **Neo-Adjuvant therapy :**Treatment as a first step to shrink a tumor before the main treatment.
- **Concurrent therapy:** When two or more therapies are given together, such as chemotherapy and radiation.

Principles of cancer chemotherapy

1. **Goal of treatment:**

- The ultimate goal of chemotherapy is cure. i.e. long term disease free survival.
- If cure is not attainable, then the goal becomes pallitation i.e. alleviation of symptoms and avoidance of life-threatening toxicity.
-

Principles of cancer chemotherapy

2. **Indications for treatment:**

- Chemotherapy is indicated when neoplasms are disseminated (Spread over a large area)and are not cured by surgery.
- Chemotherapy is also used as a supplimental treatment to attack micrometastasis following surgery and radiation treatment.

Principles of cancer chemotherapy

3. **Tumor susceptibility and growth cycle:**

- Rapidly dividing cells are generally more sensitive to anti cancer drugs. therefore the fraction of tumor cells that are in replicative stage of their cycle are most susceptible.
- Non proliferating cells (those are in Go phase) usually survive the toxic effects of many of these agents.

Principles of cancer chemotherapy

4. **Cell cycle specificity of drugs:**

- The normal and tumor cells differ in the number of cells that are in various stages of the cycle.
- Chemotherapeutic agents that are effective only against replicating cells are called cell cycle specific (CCS) drugs.
- Others are said to be cell cycle non specific (CCNS) drugs.
- The non specific drugs have more toxicity in cycling cells and are useful against tumors that have low percentage of replicating cells.

Principles of cancer chemotherapy

5. **Tumor growth rate:**

- The growth rate of most solid tumors in vivo is initially rapid, but growth rate decreases as tumor size increases. Because of unavailability of nutrients and oxygen.
- By reducing the tumor burden through surgery or radiation promotes the remaining cells growth into active proliferation and increases their susceptibility to chemotherapeutic agents.

Principles of cancer chemotherapy

6. **Treatment regimens and scheduling:**

- Drugs are administered on the bases of body surface area.
- Destruction of cancer cell by chemotherapeutic agent follows first order kinetics , i.e. given dose destroys constant fraction of cells.(Log kill)
- Combine drug therapy is more successful than single drug treatment.
- In combine therapy the drugs must have different toxicities, Mechanism of action.

Principles of cancer chemotherapy

Problems associated with chemotherapy:

- Resistance:
  a) Inherent
  b) Acquired
- Toxicities:
  Effects on normal rapidly proliferating cells i.e. Buccal mucosa, Bone marrow, GI mucosa, Hair.

Side Effects in general:

Bone marrow suppression

- Anemia
- Neutropenia
- Thrombocytopenia

- **Effects on GIT**
- Vomiting
- Stomatitis
- Dysphagia
- Constipation
- Diarrhea

Side Effects

- **Effects on skin:**
- Skin dryness
- Sunburn

- **Effects on reproductive system:**
- Decrease sperm count
- Decrease menstruation

Cell Cycle

Chemotherapeutic Agents

- **Cell Cycle Specific Drugs:**

- Antimetabolites
- Bleomycin peptide antibiotics
- Vinca alkaloids

Effective for high growth-fraction-malignancies, such as hematologic cancers.

- **Cell Cycle non-Specific Drugs:**

- Alkylating agents
- Antibiotics (Dactinomycin)
- Cisplatin

Effective for both low-growth (solid tumors) and high growth fraction malignancies

Chemotherapeutic Agents

1. **Alkylating agents:**

Cyclophosphamaide
Carboplatin
Cisplatin
Oxaliplatin
Dacarbazine

- Major interaction: Alkylation of DNA
- Binds to nucleophilic groups on various cell constituents. Including DNA
- These drugs react with carboxyl, sulfhydryl, amino, hydroxyl, and phosphate groups of cellular constituents.
- Primary DNA alkylation site: N7 position of guanine (other sites as well)
- Major Toxicity: bone marrow suppression
  - Cisplatin very little but more nausea & vomiting

Adverse Effects of Alkylating Agents

- **Myelosuppression is the dose-limiting adverse effect for alkylating agents.**
- **Nausea and vomiting are common as are teratogenesis and gonadal atrophy, although in the latter cases these are variable, according to the drug, its schedule, and route of administration.**
- **Treatment also carries a major risk of leukemogenesis and carcinogenesis.**

Chemotherapeutic Agents

2. **Antimetabolites:**

5-Fluoro-uracil
Gemcitabine
Cyterabine
Methotrexate

•Structurally related to normal compounds that exist within the cell.

•Interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.

•Their maximal cytotoxic effects are in S-phase and therefore are cell-cycle specific.

•Myelosuppression is the dose-limiting toxicity for all drugs in this class.

Chemotherapeutic Agents

Vinca Alkaloids
Vincristine
Vinblastine
Vinorelbine

Taxanes
Paclitaxel
Docetaxel

3. **Microtubule Inhibitors:**

- These are plant-derived substances .
- Cause cytotoxicity by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules.
- Vinca alkaloids inhibit microtubule polymerization and increase microtubule disassembly. The mitotic spindle apparatus is disrupted, and segregation of chromosomes in metaphase is arrested.
- Common side effects are: peripheral neuropathy, suppression of bone marrow activity, constipation, nervous system toxicity, nausea, and vomiting.

Chemotherapeutic Agents

4. **Antineoplastic Antibiotics:**

Bleomycin
Doxorubicin
Dactinomycin
Daunorubicin
Mitomycin
Actinomycin D

- Interacts with DNA, leading to disruption of DNA function.
- Also Inhibit topoisomerases (I and II) and produce free radicals.
- Cell-cycle nonspecific.
- Eg: Actinomycin D binds with double-stranded DNA and blocks the action of RNA polymerase, which prevents DNA transcription.
- Mitomycin produces delays and prolonged myelosuppression that preferentially affects platelets and leukocytes. Bleomycin very little

Chemotherapeutic Agents

Prednisone
Tamoxifen
Flutamide
Nilutamide
Bicalutamide

5. **Hormonal Agents:**

- Commonly involves the use of glucocorticoids.
- Direct antitumor effects are related to their lympholytic properties.
- Glucocorticoids can inhibit mitosis, RNA synthesis, and protein synthesis in sensitive lymphocytes.
- Tamoxifen - nonsteroidal antiestrogen
- Considered cell-cycle nonspecific .
- Resistance to a given glucocorticoid may develop rapidly and typically extends to other glucocorticoids.

Chemotherapeutic Agents

Rituximab
Trastuzumab
Cetuximab
Bevacizumab

6. **Monoclonal Antibodies:**

- Antibodies that are made in the lab rather than by a person's own immune system.
- Directed at specific targets and often have fewer adverse effects.
- Designed to recognise and find specific abnormal proteins on cancer cells.
- Each monoclonal antibody recognizes one particular protein.

Chemotherapeutic Agents

Rituximab
Trastuzumab
Cetuximab
Bevacizumab

- Three types of monoclonal A-bodies:

1. Trigger the immune system to attack and kill cancer cells. E.g. Rituximab (Mabthera)
2. Stop cancer cells from taking up proteins E.g. Trastuzumab (Herceptin).
3. Carry cancer drugs or radiation to directly to cancer cells These are called conjugated MABs.
   E.g. Ibritumomab (Zevalin)