Cancer Chemotherapy
(Cytotoxic Drugs)

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There are **six** methods to treat cancer:

1. Surgery
2. Radiotherapy
3. Chemotherapy
4. Endocrine therapy
5. Biological therapy
6. Immunotherapy

Benefit achieved with cytotoxic chemotherapy:

- **Chemosensitive cancers(could be curable)**
  e.g. seminoma, teratoma, high grade non-Hodgkin's lymphoma, Hodgkin's lymphoma, Wilms' tumour

- **Chemoresistant cancers**
  e.g. gastric cancer, pancreatic cancer, sarcoma, hepatoma, melanoma, renal cancer, bladder cancer

Cell cycle phases:

Mitosis (Division)
G1: 1st gap (resting) phase (preparing)
S phase: DNA synthesis
G2: 2nd gap phase (repair)
Mitosis

In general, cytotoxics are most effective against actively dividing cells, and least effective against resting cells.

Cytotoxic drugs can be:

a) Cell cycle *non-specific*: kill cells whether resting or actively cycling e.g. alkylating agents, doxorubicin(cytotoxic antibiotic)

b) Cell cycle (phase) *specific*: kill only cells that are actively cycling e.g. antimetabolites, vinca alkaloids

Anticancer Drugs

- Alkylating drugs
- Antimetabolites
- Antibiotics (cytotoxic antibiotics)
- Alkaloids of plant origin (vinca alkaloids)
- Adrenocorticosteroids, hormones, their antagonists and many others

Alkylating Agents
(Nitrogen mustards and ethyleneimines)

- Act by transferring alkyl groups to DNA, usually in the N-7 position of guanine during cell division forming covalent linkage between two guanines on the a single DNA strand or cross-link two DNA strands preventing their replication. The same can occur with RNA or between DNA and proteins.

- **Examples**: cyclophosphamide, ifosfamide,
  chlorambucil, melphalan, busulfan,
  mustine (mechlorethamine),
  nitrosureas (carmustine **[BCNU] and lomustine [CCNU])**
  thiotepa

Cyclophosphamide

- Not itself cytotoxic, metabolized in the body by the liver to other alkylators; the main active metabolite is phosphoramide mustard.
- Given orally or i.v.
- Plasma half-life 6-12 hours
- Renal excretion of the more polar metabolite (Acrolein) results in irritation of the bladder and chemical (hemorrhagic) cystitis

Adverse effects

- nausea and vomiting
- alopecia (marked in the young)
- cystitis (drink plenty of fluids and empty bladder frequently; this urothelial toxicity is antagonized by mesna)
- myelosuppression at 7-10 days
- significant infertility in both males and females

Urothelial toxicity commonly manifests as hemorrhagic cystitis, and is peculiar to the use of cyclophosphamide and ifosfamide

and caused by their metabolite: acrolein

Mesna (mercaptoethanesulphonate) provides free thiol groups that bind acrolein. High urine volume and mesna are used to prevent hemorrhagic cystitis particularly when high doses of cyclophosphamide and ifosfamide are used.

Antimetabolites

- Are structural analogues of normal metabolites required for cell function and replication and act by competition

Examples

- methotrexate: folic acid antagonist
- 6-mercaptopurine (6-MP): purine analogue
- cytarabine and 5- fluorouracil: pyrimidine analogues

- Antimetabolites cause GI toxicity including stomatitis and diarrhea as well as bone marrow depression

- Hepatic dysfunction potentiates the toxicity of 5-flurouracil since it is metabolized by the liver.

- 5-fluorouracil has been used in treatment of solid tumors including GIT tumours, and can be used topically for malignant skin lesions

Methotrexate (MTX)

- Is a folic acid antagonist; competitively inhibits the enzyme (dihydrofolate reductase) preventing the synthesis of tetrahydrofolic acid (folinic acid) which is essential for the synthesis of purines and pyrimidines and therefore nucleic acids.

Folinic acid rescue: folinic acid may be given 24 hours after large dose of MTX to bypass and terminates MTX action (bone marrow cells recover better than tumour cells; useful selectivity. It also protect against GI toxicity such as stomatitis and diarrhea)

- MTX can be given orally, i.v., i.m., and intrathecally
- It should be used with extreme caution in renal impairment as the kidney is its main route of excretion

- Active secretion of MTX by renal tubules is blocked by salicylates and probably other NSAIDs which also displace MTX from plasma proteins increasing risk of toxicity

Cytotoxic Antibiotics

-Interfere with DNA and/or RNA synthesis. **Examples**:

Bleomycin

The cytotoxic effect of bleomycin appears to be due to oxidative damage to DNA, leading to single and double stranded breaks.

- Bleomycin is concentrated in skin and lung tissue and has a significant cutaneous and pulmonary toxicity. On the other hand, it has only mild myelo- and immunosuppressant activities

Doxorubicin (Adriamycin)

Others e.g mitomycin and streptozotocin (the latter is used to treat islet-cell pancreatic tumours)

Alkaloids of plant origin
(Vincristine, vinblastine, vindesine)

- Inhibit microtubule assembly and cause cell cycle arrest in mitosis (spindle poisons)
- **Vincristine** causes peripheral neuropathy and minimal bone marrow suppression; **vinblastine** causes marked bone marrow suppression and minimal peripheral neuropathy

Other cytotoxic drugs

- Asparaginase
- Procarbazine
- Dacarbazine
- Platinum drugs e.g. cisplatin and carboplatin. They also cross-link DNA. Cisplatin can cause severe vomiting, nephrotoxicity and ototoxicity.
- Hydroxyurea
- Protein kinase inhibitors e.g. Axitinib
- Many others

Adverse effects of cytotoxic drugs

Cytotoxic drugs act against all cells which are multiplying rapidly:
Bone marrow, mucosal surfaces (gut), hair follicles, reticuloendothelial system, germ cells.

All dividing more rapidly than many cancers, and are also damaged by cytotoxic drugs.

Many solid tumours divide slowly and recovery from cytotoxic agents is slow, while normal marrow and gut recover rapidly. This rapid recovery is used as a basis for intermittent courses of chemotherapy.

Main adverse effects of cytotoxic drugs

- Nausea and vomiting
- Bone marrow suppression: bleeding, infection
- Gut epithelium and other mucosal surfaces: diarrhea, mouth ulcers
- Hair follicles: alopecia
- Germ cells and reproduction: sterility, teratogenesis
- Delayed wound healing
- Local toxicity if extravasation occurs
- Hyperuricemia
- Specific organ damage
- Second malignancies

Nausea and vomiting

- Common and can be severe
- May be immediate (within 1-5 hours), or delayed for several days (it could be anticipatory before the next dosing regimen)
- The most effective drugs:
    * 5-HT3 receptors antagonists: ondansetron
    * D2-dopamine antagonists: metoclopramide

  They may be used in combination with:
    * a benzodiazepine (anxiety is a major factor in promoting vomiting when the patient knows that it will occur as with cisplatin)
    * dexamethasone: unknown mechanism, probably by reducing edema around the vomiting centre.

Other drugs: prochlorperazine, domperidone, nabilone
Combinations are often more effective than a single drug e.g.

benzodiazepine plus dexamethasone plus: a 5-HT3 blocker (ondansetron) or D2- receptor blocker (metoclopramide)

Bone marrow suppression

- Is the single most important dose-limiting factor with cytotoxics
- Is associated with the twin danger of:

* **infection**: often oppportunistic by Gram-negative bacteria e.g. from the gut. Others: virus (H.zoster), fungus (candida), protozoa (pneumocystis).
* **bleeding**: due to thrombocytopenia

Bone marrow suppression could be:

- **deliberate** e.g. in treatment of leukemia
- **toxicity** which could be:
  * **rapid** e.g. nitrogen mustard, cyclophosphamide, MTX, vinblastine, ….
  * **delayed** e.g. nitrosureas (BCNU, CCNU), melphalan (for 6-12 weeks)

All cytotoxic drugs cause significant bone marrow suppression except bleomycin and vincristine. These two drugs cause no or minimal BM suppression

Alopecia (Reversible hair loss)

The most frequent offenders are: adriamycin and cyclo-phosphamide

Fertility

1. Females: do not usually have any long term effect on fertility although frequently stop menstruation
2. Males: profound reduction in sperm count particularly with alkylating agents
3. No conception should be attempted when one partner is being treated. The safe period is unknown, probably 4-6 months

Hyperuricemia

- May occur with lymphoma and leukemia
- Can be worsened by chemotherapy
- May cause acute renal failure
- Allopurinol can be started 24 hours before treating such tumors; patients should be well hydrated

- With allopurinol, the dose of mercaptopurine and azathioprine should be reduced

Endocrine Therapy

The growth of some tumours is hormone-dependent and may be inhibited by:

* administration of opposite hormones, hormone antagonist of estrogens, progestogens or androgens, or inhibitors of hormone synthesis

Examples

Tamoxifen: an estrogen-receptor antagonist. Used for breast cancer in post-menopausal women. In estrogen receptor +ve; response is 60%; in –ve response is only 10%.

Aminoglutethimide: inhibit conversion of androgens to estrogens (for breast cancer)

Gonadorelin analogues e.g. goserelin: After initial stimulation, inhibition of testesterone release occurs (for prostatic cancer)

Finasteride

An inhibitor of the enzyme 5α-reductase which activates testesterone (used in benign prostatic hypertrophy, BPH)

Adrenocorticosteroids

- Cytotoxic for cancers of lymphoid tissue and blood
- Also to treat some cancer complications such as hypercalcemia and raised intracranial pressure. It can have euphoric or mood-elevating effect and used in treatment of nausea and vomiting induced by cytotoxic drugs

Combination of anticancer therapy

- Drugs having different mechanisms of action in order to minimize drug resistance.
- Drugs with different spectra of clinical toxicity allowing administration of full doses of each drug

  Example

  MOPP for Hodgkin's lymphoma

  M = Mustine (nitrogen mustard)

  O = Oncovin (vincristine)

  P = Procarbazine

  P = Prednisolone

5- FU combined with cyclophosphamide and MTX (CMF regimen) is used for treatment of many women with breast cancer

Biological Therapy

- Naturally occurring substances which regulate cell function can be used to treat cancer

  * Interleukins which stimulate proliferation of T-lymphocytes and activate natural killer cells.
  * Interferons and cytokines can also be used.

Immunotherapy

- Non-specific stimulation of active immunity with vaccines e.g. BCG instilled into the urinary bladder for bladder cancer.
- Passive immunotherapy with monoclonal antibodies raised against specific tumour-associated antigens