Anticancer drugs

Principles of cancer chemotherapy & antimetabolites-1

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•Cancer chemotherapy aims to cause lethal cytotoxic event in cancer cell that can arrest tumor's progression.

•Almost all antitumor agents don't differentiate between normal & abnormal cells.

A. Treatment strategies:

1. Goals of treatment: The ultimate goal of chemotherapy is a cure
(that is, long-term, disease-free survival).
If a cure is not attainable: the goal becomes **control of disease** (stop the cancer from enlarging and spreading) to extend survival & maintain the best quality of life.

2. Indications for treatment:

- **Chemotherapy is indicated when neoplasms are spreading.**

- **Adjuvant: supplemental treatment to attack micrometastases.**

- **Neoadjuvant: prior to surgical procedure to shrink the cancer.**

- **Maintenance: lower doses to assist in prolonging a remission.**

3. Tumor susceptibility and the growth cycle:

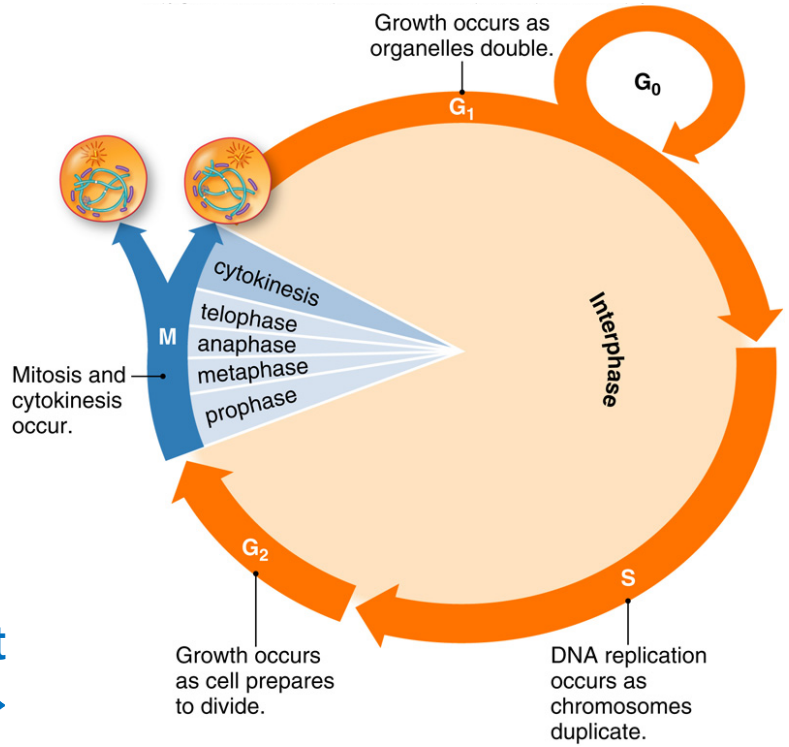
Rapidly dividing cells are more sensitive to anticancer drugs, while slowly proliferating cells (those in G_0 phase) are less sensitive to chemotherapy.

a- Cell-cycle specificity of drugs

- *Cell cycle specific (act on replicating cells)*
- *Cell cycle non-specific (can act on non-replicating cells*

b- Tumor growth rate

As tumor grows→ vascularity can't supply O_2 & nutrients → slow growing → non-responsive. So, remove part of tumor → rapid proliferation → sensitive to ttt.



B. Treatment regimens and scheduling:

Tailoring is done based on body surface area.

Treatment protocols:

a. Combinations of drugs: higher response rates, due to additive and/or potentiated cytotoxic effects, and non-overlapping host toxicities.

b. Advantages of drug combinations:

1. **Provide maximal cell killing within the range of tolerated toxicity**
2. **Effective against a broader range of cell lines**
3. **May delay or prevent the development of resistant cell lines.**

C. Problems associated with chemotherapy:

They are toxins that present lethal threat to cells. Therefore, cells have evolved defense mechanisms to protect themselves.

1. **Resistance: Some neoplastic cells (e.g. melanoma) are inherently resistant to most anticancer drugs.**

- **Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutation, particularly after prolonged administration of suboptimal drug doses.**

- **The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs.**

2. **Toxicity:** Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation **(e.g. buccal mucosa, bone marrow, GI mucosa, and hair follicles),** contributing to the toxic manifestations of chemotherapy.
3. **Treatment-induced tumors:** because most drugs are mutagens (e.g.: alkylating agents)

Antimetabolites

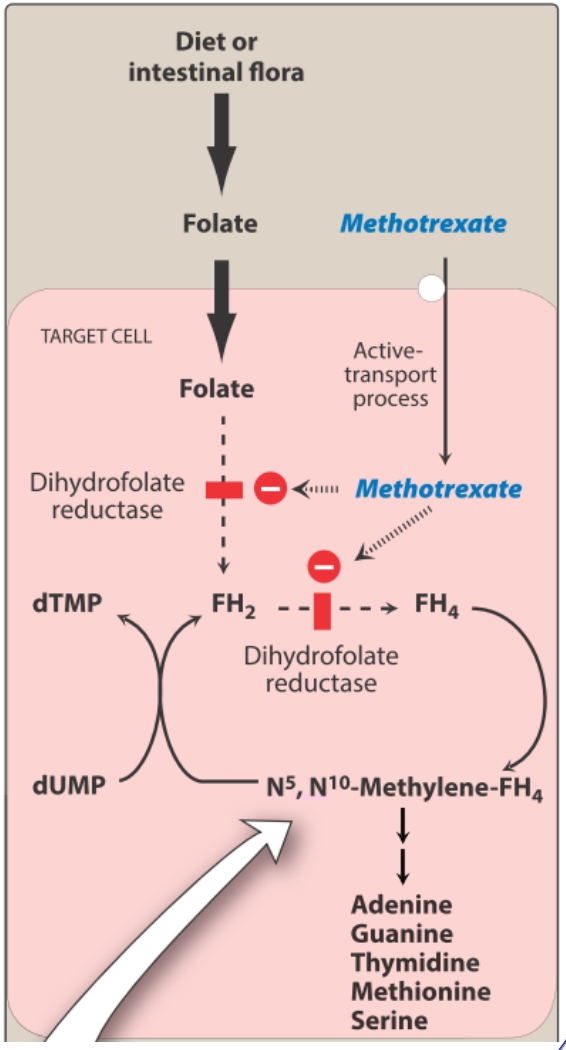
- **Antimetabolites are structurally related to normal compounds that exist within the cell.**

- **They generally 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.**

Methotrexate

Mechanism of action

- Methotrexate (MTX) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting DHFR (dihydrofolate reductase), which is the enzyme that converts folic acid to its active, coenzyme form, THF (tetrahydrofolate).
- This leads to depressed DNA, RNA, and protein synthesis and, ultimately, to cell death.



Methotrexate

Therapeutic uses

- MTX, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma (Uterus), Burkitt lymphoma in children (lymph nodes), breast cancer, and head and neck carcinomas.
- In addition, low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn's disease.
- All patients receiving MTX require close monitoring for possible toxic effects.

6-Mercaptopurine

Mechanism of action

a. Nucleotide formation: To exert its antileukemic effect, 6-MP must penetrate target cells and be converted to the nucleotide analog.

b. Inhibition of purine synthesis: A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog.

c. Incorporation into nucleic acids: nucleotide analog can be incorporated into RNA & DNA → nonfunctional RNA and DNA.

5-Fluorouracil

- Pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom.
- The fluorine interferes with thymidine synthesis, one of the essential precursors for DNA synthesis.
- 5-FU is employed primarily in the treatment of slowly growing solid tumors (e.g. colorectal, breast, ovarian, pancreatic, and gastric carcinomas).
- When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

Capecitabine

- **Novel drug approved for the treatment of metastatic breast cancer that is resistant to first-line drugs (e.g. paclitaxel and anthracyclines) and is currently also used for treatment of colorectal cancer.**

Floxuridine

- **Interferes with the synthesis of DNA and, to a lesser extent, inhibit the formation of RNA.**
- **Floxuridine is effective in the palliative (*soothing*) management of gastrointestinal adenocarcinoma that has metastasized to the liver.**

Gemcitabine

- **First-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas.**
- **It also is effective against non–small cell lung cancer and several other tumors.**