Cancer Chemotherapy

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Cancer chemotherapy

- Growth fraction
- Proliferating cells , Non-proliferating cells
- Mechanisms of Antineoplastic Drugs
- Toxicity of Antineoplastic Drugs
- Classification of Antineoplastic Drugs

phase of proliferation cycle
source and action mechanisms

- Principles of combination therapies

General Introduction

- Cancers account for 20-25% of deaths in clinical practices.
- Attempts to cure or palliate cancer employ 3 principal methods: *operation, radiotherapy, and chemotherapy.*
- Differing from the operation and radiotherapy that emphasize on the treatment of local tissues, *the chemotherapy is concerned with that of the whole body.*

Cancer chemotherapy

- Chemotherapy is the use of drugs to inhibit or kill proliferating cancer cells, while leaving host cells unharmed, or at least recoverable.

Growth fraction

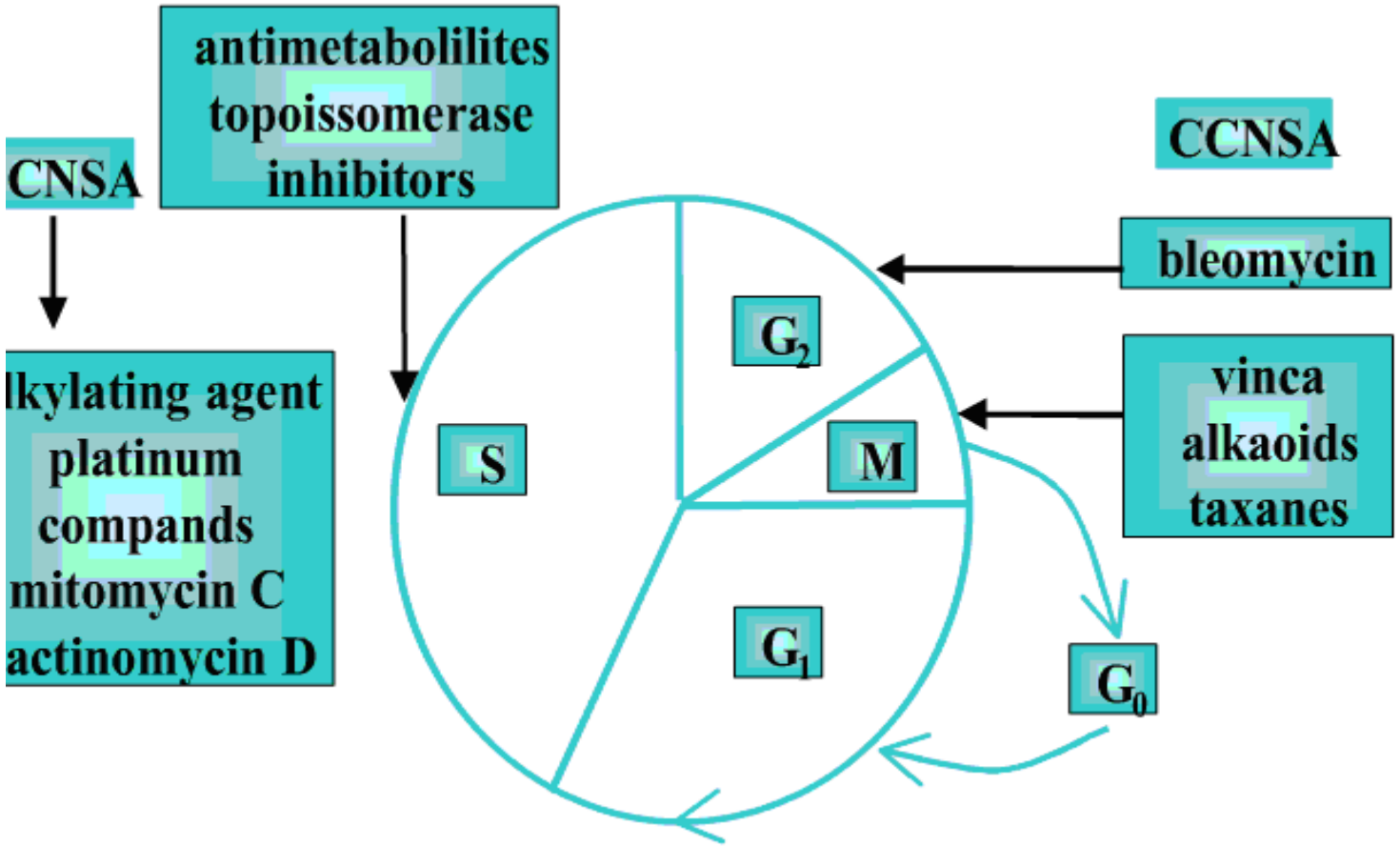
- Tumor cells can be classified as *proliferating cells* and *non-proliferating cells*.
- The ratio of proliferating cells in the whole tumor tissue is called growth fraction (GF).
  - The faster the tumor cells proliferate, the bigger the GF is and the higher the sensitivity of tumor to a drug is.
  - Generally, *in the early stage, the GF of a tumor is bigger and the effect of a drug on the tumor is better*.

q Proliferating cells

Based on the DNA changes in cells, proliferating cycle of tumor cells can be divided into 4 phases

- Pre-synthetic phase (Gap 1 phase or G1 phase). cells chiefly make preparations for the synthesis of DNA.
- Synthetic phase (S phase). cells are synthesizing their DNA.
- Post-synthetic phase (Gap 2 phase or G2 phase). DNA duplication has been finished and they are equally divided to the two of future sub-cells.
- Mitosis phase (M Phase). each cell is divided into two sub-cells. Some of these new cells enter the new proliferating cycle, the others become non-proliferating cells.

q Proliferating cells



Non-proliferating cells

- Non-proliferating cells include *G_0 phase cells* (resting-phase cells),
- G_0 phase cells have proliferation ability but do not divide temporally.
- When proliferating cells are suffered heavy casualties, G_0 phase cells will get into proliferating cycle and become the reasons of tumor recurrence.
- G_0 phase cells are usually *not sensitive to antineoplastic drugs*, which is the important obstacle to tumor chemotherapy.

Cancer chemotherapy

- **Growth fraction**
- **Proliferating cells , Non-proliferating cells**
- **Mechanisms of Antineoplastic Drugs**

  - Ø destruction of DNA or inhibition of DNA duplication
  - Ø inhibition of nucleic acid (DNA and RNA) synthesis
  - Ø Interfering with the transcription to inhibit RNA synthesis
  - Ø Inhibition of protein synthesis
  - Ø Interfering with hormone balance

- **Toxicity of Antineoplastic Drugs**
- **Classification of Antineoplastic Drugs**
- **Principles of combination therapies**

Mechanisms of Antineoplastic Drugs

Most antineoplastic drugs act on the proliferating cycle of cell

(1) *destruction of DNA or inhibition of DNA duplication*

- e.g. alkylating agents, mitomycin C

(2) *inhibition of nucleic acid (DNA and RNA) synthesis*

- e.g. 5-fluorouracil, 6-mercaptopurine, methotrexate, cytarabine, etc.

Mechanisms of Antineoplastic Drugs

(3) *Interfering with the transcription to inhibit RNA synthesis*

- e.g. dactinomycin, dauoruicin, and doxorubicin

(4) *Inhibition of protein synthesis*

- e.g. vinca alkaloids, epipodophylotoxins, and paclitaxel

(5) *Interfering with hormone balance*

- e.g. adrenal corticosteroids, estrogens, tamoxifen etc.

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Toxicity of Antineoplastic Drugs

Short-term toxicity

- Common side reactions usually appear earlier and many of them occur in rapid-proliferating tissues such as marrow, gastrointestinal tract, and hair follicle.
  - myelosuppression,
  - gastrointestinal tract symptom
  - alopecia

Toxicity of Antineoplastic Drugs

Long-term toxicity

- The long-term toxicity mainly occurs in the patients who received chemotherapy many years ago.
  - Examples: carcinogenesis, teratogenesis and sterility.

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Classification of Antineoplastic Drugs

- On the basis of antineoplastic action on the phase of proliferation cycle, drugs are classified as
  - ***cell cycle non-specific agents*** (phase non-specific agents, CCNSA) (e.g. alkylating agents)
    - Act in all proliferating phases, even the G_0
    - effects are stronger.
  - ***cell cycle specific agents*** (phase specific agents, CCSA). (e.g. Antimetabolites, vinca alkaloids)
    - just act on specific phases of the cell cycle
    - effects are comparatively weaker.

Classification of Antineoplastic Drugs

- On the basis of source and action mechanisms, the drugs are also classified as:
  - alkylating agents,
  - antimetabolites,
  - natural products,
  - hormones and antagonists
  - miscellaneous agents.

(Ⅰ) Alkylating Agents

- Alkylating agents act via a reactive alkyl (R-CH_2-CH_2^+ -) group that reacts to form covalent bonds with nucleic acids.
- There follows either cross-linking of the two strands of DNA, preventing replication, or DNA breakage.
  - All alkylating agents are phase-nonspecific.
  - kill rapidly proliferating cells, also kill non-proliferating cells.

(Ⅰ) Alkylating Agents

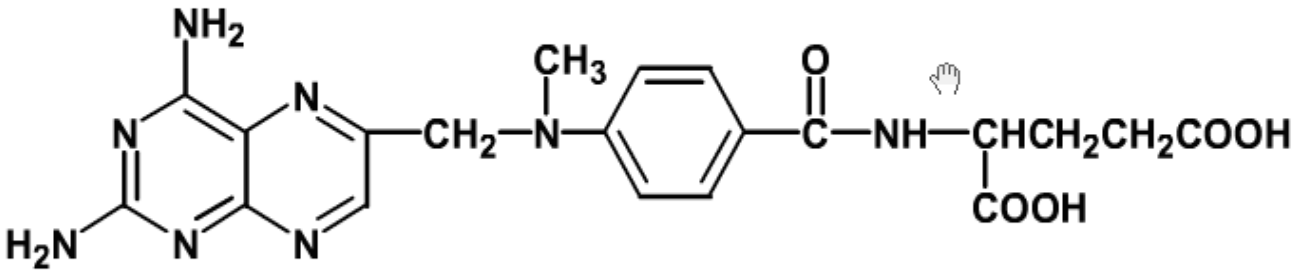
- Examples: Mechlorethamine
  - the first drug used in the treatment of cancer
  - At present, it is mainly used for Hodgkin's disease and non-Hodgkin's lymphomas.
- Examples: Cyclophosphamide
  - Most widely used in clinical therapy for treatment of cancer at present.
  - It has no antineoplastic action outside the body and must be activated in the liver

(Ⅱ) Antimetabolites

- Antimetabolites are analogues of normal metabolites and act by competition, replacing the natural metabolite and then subverting cellular processes.
- Examples of antimetabolites include:
  - Folic acid antagonists (e.g. Methotrexate).
  - Antipyrimidines (e.g. 5-Fluorouracil, Cytarabine).
  - Antipurines (e.g. 6-Mercaptopurine)

(Ⅱ) Antimetabolites

- 甲氨蝶呤　Methotrexate



(Ⅱ) Antimetabolites

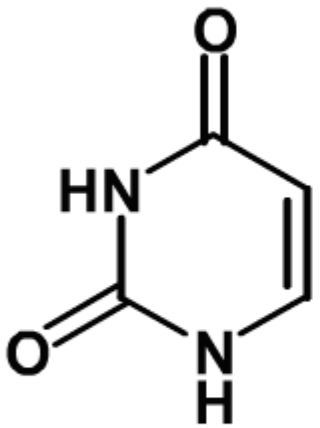
- Example: methotrexate
  - Mimics folic acid, which is needed for synthesis of DNA, RNA and some amino acids
  - It acts mainly on the S phase cells.
  - has a serious myelosuppression

(Ⅱ) Antimetabolites

- Example: 6-Mercaptopurine
  - A structural analogue of hypoxanthin
  - It must be converted intracellularly to the nucleotide 6-mercaptopurine ribose phosphate and 6-methylmercaptopurine ribonucleotide, and then inhibit purine biosynthesis, causing inhibition of biosynthesis of nucleic acid.

(Ⅱ) Antimetabolites

- 氟尿嘧啶 Fluorouracil



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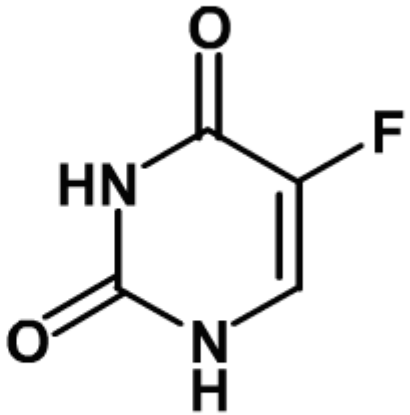

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(Ⅱ) Antimetabolites

- Example: 5-Fluorouracil (5-FU)
  - a flurorine-substituted analogue of uracil
  - must be metabolically activated to a nucleotide, in this case FdUMP.
  - then its metabolite inhibits the synthetase of deoxythymidine monophosphate, blocking DNA synthesis. Besides, as the fraudulent substance, its metabolite can also interfere with the synthesis of RNA.
  - a phase-specific drug.

(Ⅲ) Natural Products

- This group is determined by the source of the drug
- The major classes of natural products include
  - antibiotics
  - vinca alkaloids
  - biologic response modifiers
  - enzymes
  - epipodophyllotoxins
  - taxanes

(Ⅲ) Natural Products

- Antibiotic antineoplastic agents
  - Damage DNA in cycling and noncycling cells
- Example: Dactinomycin (actinomycin D)

This drug binds noncovalently to double-stranded DNA and inhibits DNA-directed RNA syntheisis. Dactinomycin is **a phase-nonspecific agent**, but it is more active agsinst G1 phase cells.

(Ⅲ) Natural Products

- Vinca (plant) alkaloids
  - Vincristine and vinblastine are alkaloids derived from the periwinkle plant.
  - binding to tubulin, interfere with the assembly of spindle proteins during mitosis..
  - Act in M phase to inhibit mitosis, blocking proliferating cells as they enter metaphase.
  - Both can cause bone marrow suppression and neurotoxicity

(Ⅳ) Hormones and antagonists

- The growth of some cancers is hormone dependent. Growth of such cancers can be inhibited by surgical removal of hormone glands, increasingly, however, administration of hormones or antihormones is preferred.

(Ⅳ) Hormones and antagonists

Examples:

- Adrenocortical steroids to inhibit the growth of cancers of lymphoid tissue and blood.
- Oestrogen antagonists (tamoxifen) is indicated for breast cancer.
- Oestrogen is used for prostatic cancers.

(Ⅴ) Miscellaneous agents

- Examples: Hydroxyurea
  - Hydroxyurea inhibits ribonucleotide reductase. inhibition of DNA synthesis.
  - It is specific for the cells of **S** phase
  - The major adverse effect of this drug is bone marrow depression.

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1. Select drugs according to their phase specific characteristics
2. Combinations of antineoplastic drugs with different action mechanism
3. Combinations of antineoplastic drugs with other therapies
5. Select drugs according to antineoplastic range (spectrum)
6. Use right dose

Principles of combination therapies

- In order to enhance curative effect, to decrease the toxicity and to reduce the drug resistance, combination therapies are often used in the treatment.
- Advantages of drug combinations:
  - They provide maximal cell kill within the range of tolerated toxicity.
  - They are effective against a broader range of cell-cycle phases.
  - They may slow or prevent the development of resistance.

Principles of combination therapies

1. Select drugs according to their phase specific characteristics
   - The aim of this rule is to urge more G_0 phase cells to enter the proliferating cycle so as to increase the amount of tumor cells killed by drugs.

Principles of combination therapies

- For high GF tumor such as acute leukemia, phase specific drugs are firstly used to kill S or M phase cells, and then phase non-speicfic drugs are used to kill tumor cells in other phases, and finally the above two steps are repeated once again to kill new cell from G_0 phase.
- For low GF tumor such as solid tumors, phase non-specific drugs are firstly used to kill cells of all phases, and then phase specific drugs are used, and finally the above steps are repeated to kill the new cell from G0 phses.

Principles of combination therapies

2. Combinations of antineoplastic drugs with different action mechanisms.
   - can destroy tumor cells from various biochemical links at same time.

3. Combinations of antineoplastic drugs with other therapies
   - Examples: chemotherapy plus operation,
     chemotherapy plus radiotherapy.

Principles of combination therapies

4. Combination of low-toxic drugs with high-toxic ones

- does not obviously increase the toxicity of antineoplastic drugs while the remarkable synergism of anticancer action is produced.
- Example: bleomycin (light myelosuppression) + mitomycin (serious myelosuppression), which is often used to treat carcinoma of cervix.

Principles of combination therapies

5. Select drugs according to antineoplastic range (spectrum)

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Thank you!!