Chemotherapeutic Agents

Introduction To Chemotherapeutic Agents

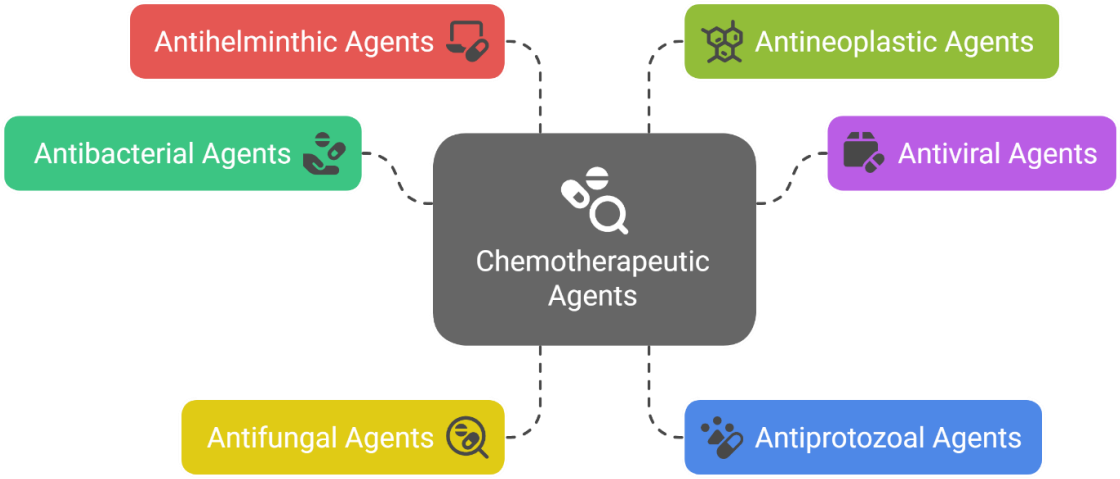
Definition:

- Chemotherapeutic agents are chemical substances used to destroy or inhibit the growth of pathogenic organisms or neoplastic (cancerous) cells **without causing significant damage to the host.**
    - **Antimicrobial chemotherapy** targets **infectious organisms** (bacteria, viruses, fungi, protozoa, helminths).
    - **Antineoplastic chemotherapy** targets **malignant cells** in cancers.

Historical Perspective:

- **Paul Ehrlich** (early 1900s): Father of chemotherapy. Coined the term “magic bullet” for selective targeting.
- **Sulfonamides** (1930s): First synthetic antibacterial agents.
- **Penicillin** (1928–1940s): First antibiotic, discovered by Alexander Fleming.

Types of Chemotherapeutic Agents:



- **Antibacterial agents:** Penicillins, cephalosporins, aminoglycosides, etc.
- **Antiviral agents:** Acyclovir, zidovudine, oseltamivir.
- **Antifungal agents:** Amphotericin B, fluconazole.
- **Antiprotozoal agents:** Chloroquine, metronidazole.
- **Antihelminthic agents:** Albendazole, mebendazole.
- **Antineoplastic agents:** Cyclophosphamide, vincristine, methotrexate, cisplatin.

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Basic Principles of Chemotherapy of Infections

Selective Toxicity

- The core principle of antimicrobial therapy. Agents should:
    - Kill or inhibit pathogens
    - Cause minimal harm to the host, This is achievable due to structural and metabolic differences between microbial and human cells (e.g., bacterial cell walls, unique enzymes, ribosomes).

Spectrum of Activity

- **Narrow-spectrum agents**: Target specific organisms (e.g., Penicillin G targets Gram-positive bacteria).
- **Broad-spectrum agents**: Effective against a wide range, including both Gram-positive and Gram-negative bacteria (e.g., tetracyclines).

Bacteriostatic vs Bactericidal

- **Bacteriostatic**: Inhibit growth and reproduction (e.g., tetracycline).
- **Bactericidal**: Kill bacteria directly (e.g., penicillin).
  Choice depends on the infection site and patient's immune status.

Mechanisms of Action

- Antimicrobials target:
    - **Cell wall synthesis** (e.g., β-lactams)
    - **Protein synthesis** (e.g., aminoglycosides, macrolides)
    - **Nucleic acid synthesis** (e.g., fluoroquinolones)
    - **Cell membrane integrity** (e.g., polymyxins)
    - **Metabolic pathways** (e.g., sulfonamides)

Resistance

- Resistance arises through:
    - Mutations in drug targets
    - Drug inactivation (e.g., β-lactamases)
    - Efflux pumps
    - Decreased permeability

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- Biofilm formation, **Antimicrobial stewardship** is key to limiting resistance.

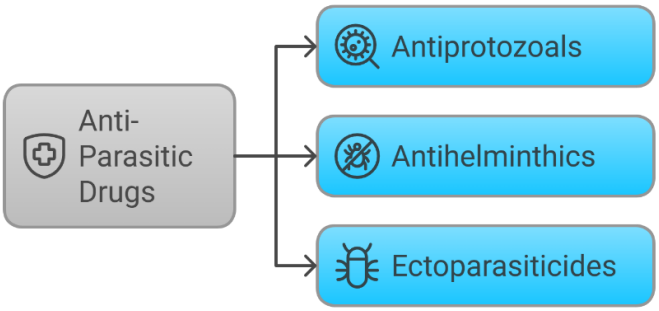
Pharmacokinetics & Pharmacodynamics

- Factors affecting drug efficacy:
  - **Absorption** (oral, IV)
  - **Distribution** (e.g., blood-brain barrier penetration)
  - **Metabolism and excretion**
  - **Time-dependent killing** (e.g., β-lactams)
  - **Concentration-dependent killing** (e.g., aminoglycosides)

Chemotherapy of Infestations

- "Infestations" typically refer to infections caused by **parasitic organisms**, including:
  - **Protozoa** (e.g., Plasmodium spp. causing malaria)
  - **Helminths** (worms like Ascaris, Schistosoma)
  - **Ectoparasites** (e.g., lice, mites)

Key Classes of Anti-Parasitic Drugs:



1. Antiprotozoals:

- **Metronidazole** (for amoebiasis, giardiasis)
- **Chloroquine, artemisinin** (for malaria)

2. Antihelminthics:

- **Albendazole, mebendazole** (broad-spectrum against nematodes)
- **Praziquantel** (against schistosomes and other flukes)

3. Ectoparasiticides:

- **Permethrin** (for scabies, lice)
- **Ivermectin** (also effective against nematodes)

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Principles:

- **Targeting unique parasite physiology**: For example, interfering with microtubule formation in worms (albendazole) or heme metabolism in Plasmodium (chloroquine).
- **Host safety** is crucial: Many antiparasitic drugs have a narrow therapeutic index.

Chemotherapy of Neoplastic Diseases (Cancer)

Basic Concepts

- Cancer involves uncontrolled proliferation of abnormal cells. Antineoplastic drugs:
  - Kill or inhibit cancer cell growth
  - Preferentially target rapidly dividing cells (including some normal cells)

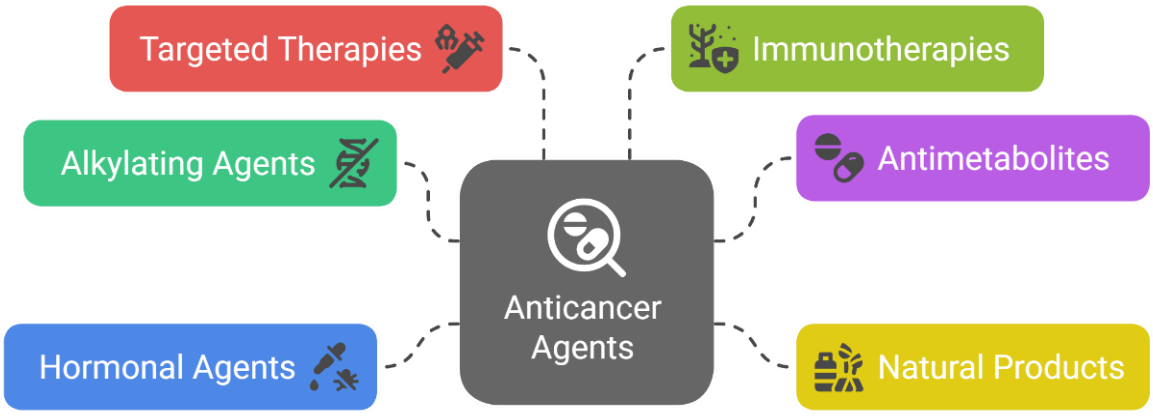
Characteristics of Antineoplastic Agents

- Not cancer-cell specific; also affect normal fast-dividing cells (e.g., bone marrow, GI tract, hair)
- Used in **combinations** to enhance efficacy and reduce resistance
- Have **narrow therapeutic indices** and significant toxicities

Cell Cycle Considerations

- **Cell-cycle specific drugs**: Act in certain phases (e.g., antimetabolites in S-phase)
- **Cell-cycle nonspecific drugs**: Act in all phases (e.g., alkylating agents)

Classes of Anticancer Agents



- **Alkylating agents** (e.g., cyclophosphamide): DNA crosslinking → apoptosis
- **Antimetabolites** (e.g., methotrexate, 5-FU): Inhibit DNA/RNA synthesis
- **Natural products**:

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  - Vinca alkaloids: Inhibit microtubules
  - Taxanes: Stabilize microtubules
  - Topoisomerase inhibitors (e.g., etoposide)
  - Antitumor antibiotics (e.g., doxorubicin): DNA intercalation, free radicals
- **Hormonal agents**:
  - Tamoxifen (breast cancer)
  - Flutamide (prostate cancer)
- **Targeted therapies**:
  - Monoclonal antibodies (e.g., trastuzumab – HER2+)
  - Tyrosine kinase inhibitors (e.g., imatinib – CML)
- **Immunotherapies**:
  - Checkpoint inhibitors (e.g., pembrolizumab – anti-PD-1)
  - CAR T-cell therapy
- **Others**: Differentiating agents (e.g., all-trans retinoic acid in APL)

Principles of Combination Chemotherapy

- Combine drugs with:
  - Different mechanisms
  - Non-overlapping toxicities
  - Distinct resistance mechanisms
- **Goal**: Maximal tumor kill, minimal host toxicity

Adverse Effects

- Due to action on all rapidly dividing cells:
  - **Bone marrow suppression**: Anemia, neutropenia, thrombocytopenia
  - **GI toxicity**: Nausea, vomiting, mucositis
  - **Alopecia**
  - **Immunosuppression** → infection risk
  - **Organ-specific toxicities**:
    - Cardiotoxicity (doxorubicin)
    - Nephrotoxicity (cisplatin)

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