

Oncology

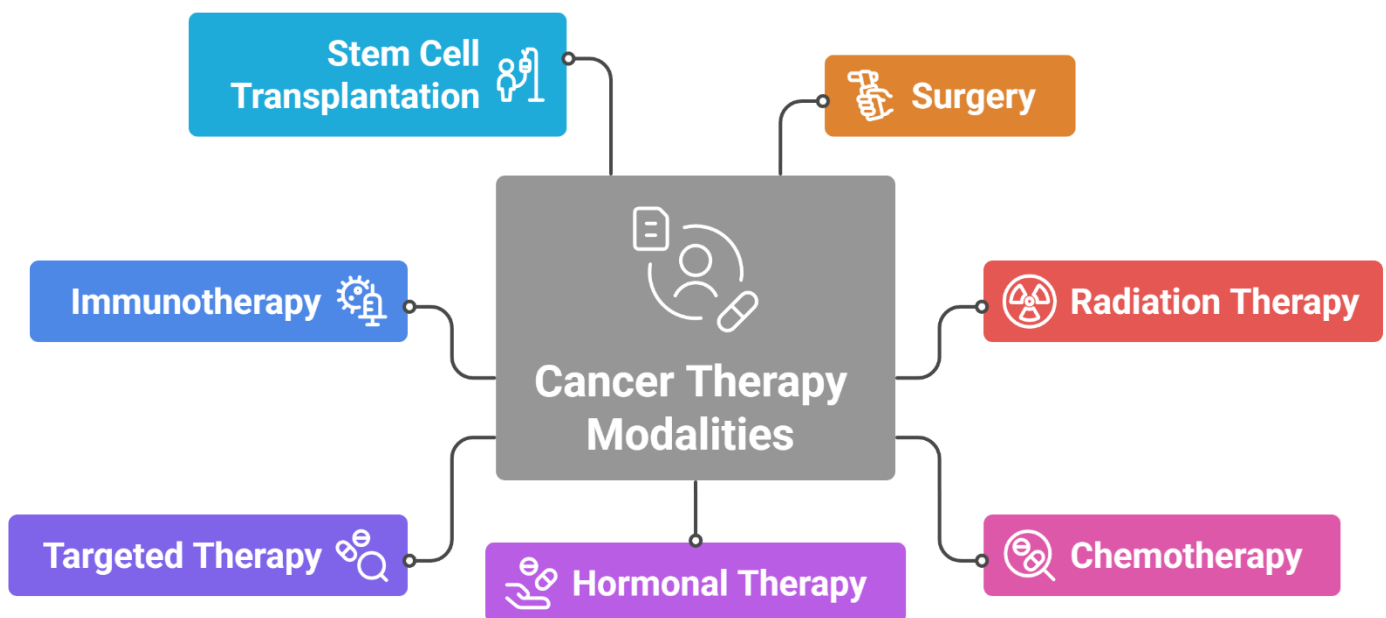
Basic Principles of Cancer Therapy

- Cancer therapy (also called **oncologic therapy**) involves various treatment modalities designed to target and eliminate malignant cells.
- The choice of therapy depends on the type of cancer, stage, patient health status, molecular profile of the tumor, and more.
- The fundamental principles aim to achieve **maximum tumor cell kill** with **minimum damage** to normal tissue.

Objectives of Cancer Therapy

1. **Curative Therapy:** The aim is complete eradication of cancer. Most effective in early-stage cancers.
2. **Palliative Therapy:** Aims to relieve symptoms and improve quality of life in advanced cancers.
3. **Adjuvant Therapy:** Given **after** primary treatment (like surgery) to kill microscopic residual disease.
4. **Neoadjuvant Therapy:** Given **before** surgery to shrink the tumor and make it operable.

Major Modalities of Cancer Therapy



1. Surgery

- Used in localized tumors.
- May be curative (e.g., early-stage colon cancer).
- Also used for tumor debulking (removing bulk to enhance effectiveness of other treatments).

2. Radiation Therapy

- Uses ionizing radiation to kill cells by inducing DNA damage.
- Works best in tumors with high radiosensitivity (e.g., lymphomas).
- Can be external beam or brachytherapy (internal).

3. Chemotherapy

- Use of cytotoxic drugs that kill rapidly dividing cells.
- Acts systemically, so it is useful for disseminated (spread) disease.
- Divided into **cell cycle-specific** and **cell cycle-nonspecific** agents.

4. Hormonal Therapy

- For cancers driven by hormones (e.g., breast, prostate cancer).
- Works by blocking hormone production or action.

5. Targeted Therapy

- Drugs designed to target specific molecular markers (e.g., EGFR, HER2).
- Less toxic to normal cells.

6. Immunotherapy

- Stimulates the immune system to recognize and kill cancer cells.
- Includes checkpoint inhibitors, CAR T-cell therapy, cytokines.

7. Stem Cell Transplantation

- For hematologic malignancies.
- Allows use of high-dose chemotherapy followed by stem cell rescue.

Key Principles in Designing Cancer Therapy

1. Combination Therapy

- Uses drugs with different mechanisms.
- Reduces the chance of drug resistance.
- Example: ABVD for Hodgkin lymphoma.

2. Dose-Response Relationship

- Many chemotherapeutic agents have a steep dose-response curve.
- Maximum tolerated dose (MTD) is often used.

3. Dose Scheduling

- Based on tumor growth kinetics (Gompertzian model).
- Intervals must allow normal tissue recovery but not enough time for tumor regrowth.

4. Tumor Heterogeneity

- Tumors consist of different cell populations.
- Therapy must target various clones.

5. Resistance

- Can be primary (intrinsic) or acquired (develops over time).
- Resistance mechanisms include drug efflux pumps (e.g., P-glycoprotein), mutations, enhanced DNA repair.

6. Toxicity to Normal Tissues

- Particularly those with high turnover: bone marrow, GI mucosa, hair follicles.
- Monitoring and managing side effects are crucial.

Treatment Planning

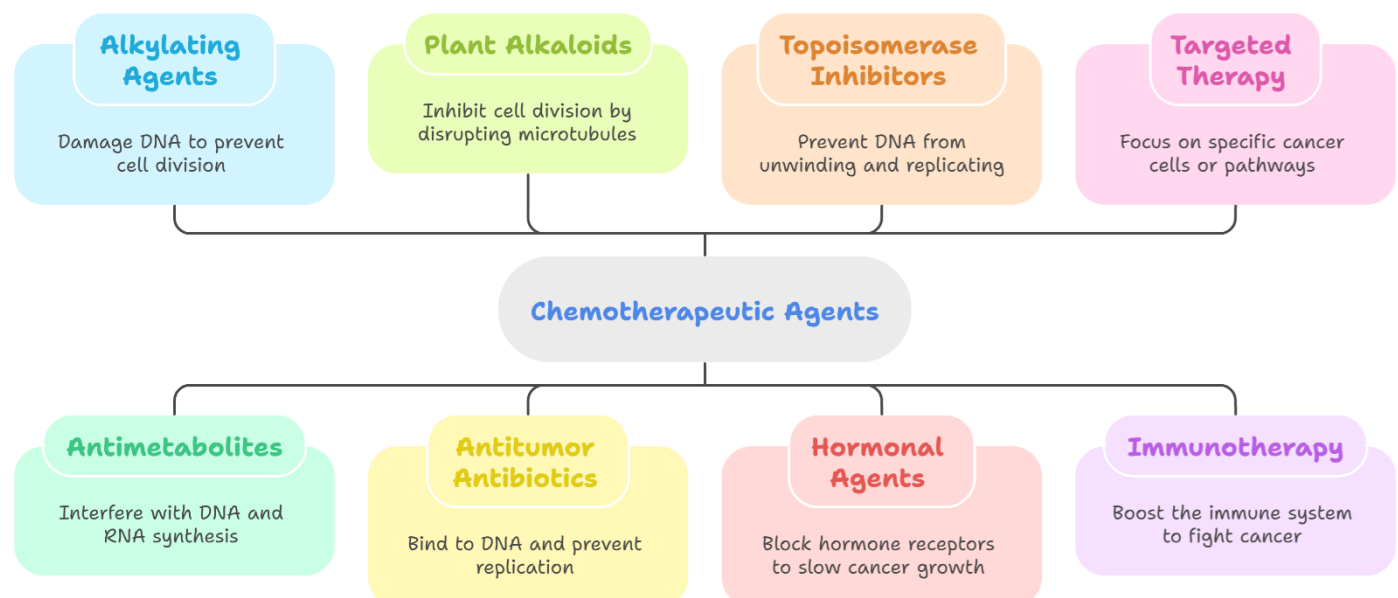
- Based on **TNM staging**, **performance status (e.g., ECOG scale)**, and **biomarkers**.
- **Multidisciplinary Tumor Boards** often decide treatment plans.
- **Neoadjuvant therapy**: Given before surgery to shrink tumors.
- **Adjuvant therapy**: Given after surgery to eliminate residual disease.

General Introduction to Cancer Chemotherapeutic Agents

- Chemotherapy refers to the use of **cytotoxic drugs** that kill or inhibit the growth of **rapidly dividing cells**, which includes both cancerous and normal cells (like bone marrow or gut epithelium).

Classification of Chemotherapeutic Agents

Chemotherapeutic agents can be broadly classified based on **mechanism of action** and **cell-cycle specificity**.



A. Alkylating Agents

- **Mechanism:** Add alkyl groups to DNA, causing crosslinking and strand breaks → inhibits DNA replication.
- **Cell Cycle:** Non-specific.
- **Examples:**
 - Cyclophosphamide
 - Ifosfamide
 - Busulfan
 - Melphalan
- **Toxicity:** Myelosuppression, hemorrhagic cystitis (cyclophosphamide due to acrolein metabolite).

B. Antimetabolites

- **Mechanism:** Mimic or inhibit natural metabolites required for DNA/RNA synthesis.
- **Cell Cycle:** S-phase specific.
- **Examples:**
 - Methotrexate (folate analog)
 - 5-Fluorouracil (pyrimidine analog)
 - Cytarabine
 - 6-Mercaptopurine (purine analog)
- **Toxicity:** Myelosuppression, mucositis.

C. Plant Alkaloids (Mitotic Inhibitors)

- **Mechanism:** Interfere with microtubule dynamics → inhibit mitosis.
- **Cell Cycle:** M-phase specific.
- **Subtypes:**
 - **Vinca Alkaloids** (e.g., vincristine, vinblastine): inhibit microtubule assembly.
 - **Taxanes** (e.g., paclitaxel, docetaxel): stabilize microtubules, preventing disassembly.
- **Toxicity:** Peripheral neuropathy (vincristine), myelosuppression (vinblastine).

D. Antitumor Antibiotics

- Derived from Streptomyces species.
- **Mechanism:** Intercalate DNA, generate free radicals, inhibit topoisomerase II.
- **Examples:**
 - Doxorubicin (anthracycline)

- Daunorubicin
- Bleomycin
- **Toxicity:**
 - Doxorubicin: cardiotoxicity.
 - Bleomycin: pulmonary fibrosis.

E. Topoisomerase Inhibitors

- **Mechanism:** Inhibit topoisomerases involved in DNA replication.
- **Examples:**
 - Topotecan, irinotecan (topoisomerase I inhibitors)
 - Etoposide (topoisomerase II inhibitor)
- **Toxicity:** Myelosuppression, diarrhea (especially irinotecan).

F. Hormonal Agents

- Used for hormone-sensitive cancers.
- **Examples:**
 - Tamoxifen (SERM) – for breast cancer
 - Anastrozole (aromatase inhibitor)
 - Flutamide (anti-androgen)
 - Leuprolide (GnRH agonist)
- **Toxicity:** Varies by agent; thromboembolism (tamoxifen), osteoporosis (aromatase inhibitors).

G. Targeted Therapy

- Targets specific molecular pathways involved in tumor growth.
- **Examples:**
 - Imatinib (BCR-ABL in CML)
 - Trastuzumab (HER2 in breast cancer)
 - EGFR inhibitors (erlotinib)
- **Toxicity:** Generally less severe than traditional chemo; specific to target (e.g., cardiotoxicity in trastuzumab).

H. Immunotherapy

- Checkpoint inhibitors: Nivolumab, pembrolizumab (PD-1 inhibitors)
- CAR-T cell therapy
- Cytokines (IL-2, IFN-alpha)



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