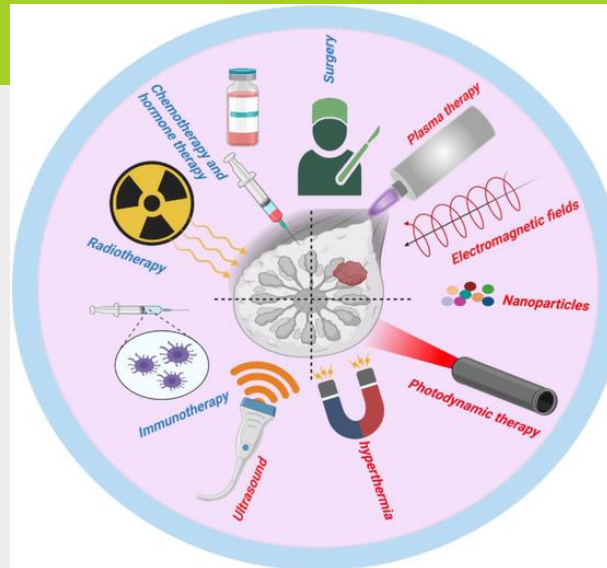
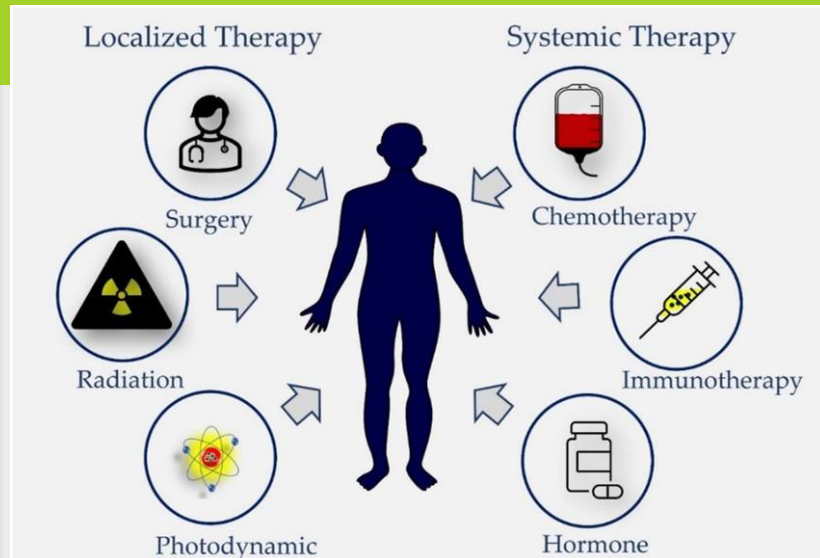


Cancer : Treatment Modalities & Principles Of Cancer Chemotherapy



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Neoadjuvant Therapy (Before Surgery/Radiation)

- Systemic therapy given before surgery or radiation.
- Indication:
 - To shrink tumor burden
 - To eradicate micrometastases early.
 - To allow for less invasive surgery (e.g., breast-conserving surgery).

Commonly used in: Breast cancer, rectal cancer, some sarcomas.

Adjuvant Therapy (Post-Surgery/Radiation)

- Systemic therapy given after local treatment (surgery/radiation).
- To eradicate micrometastatic disease (invisible, undetectable spread).
- To reduce recurrence and improve long-term survival.
- Indicated for:
 - Patients with potentially curable cancers.
 - No clinically detectable disease after surgery/radiation.
- Effectiveness measured by:
 - Recurrence rates.
 - Overall survival, since disease is not measurable.

Curative Treatment

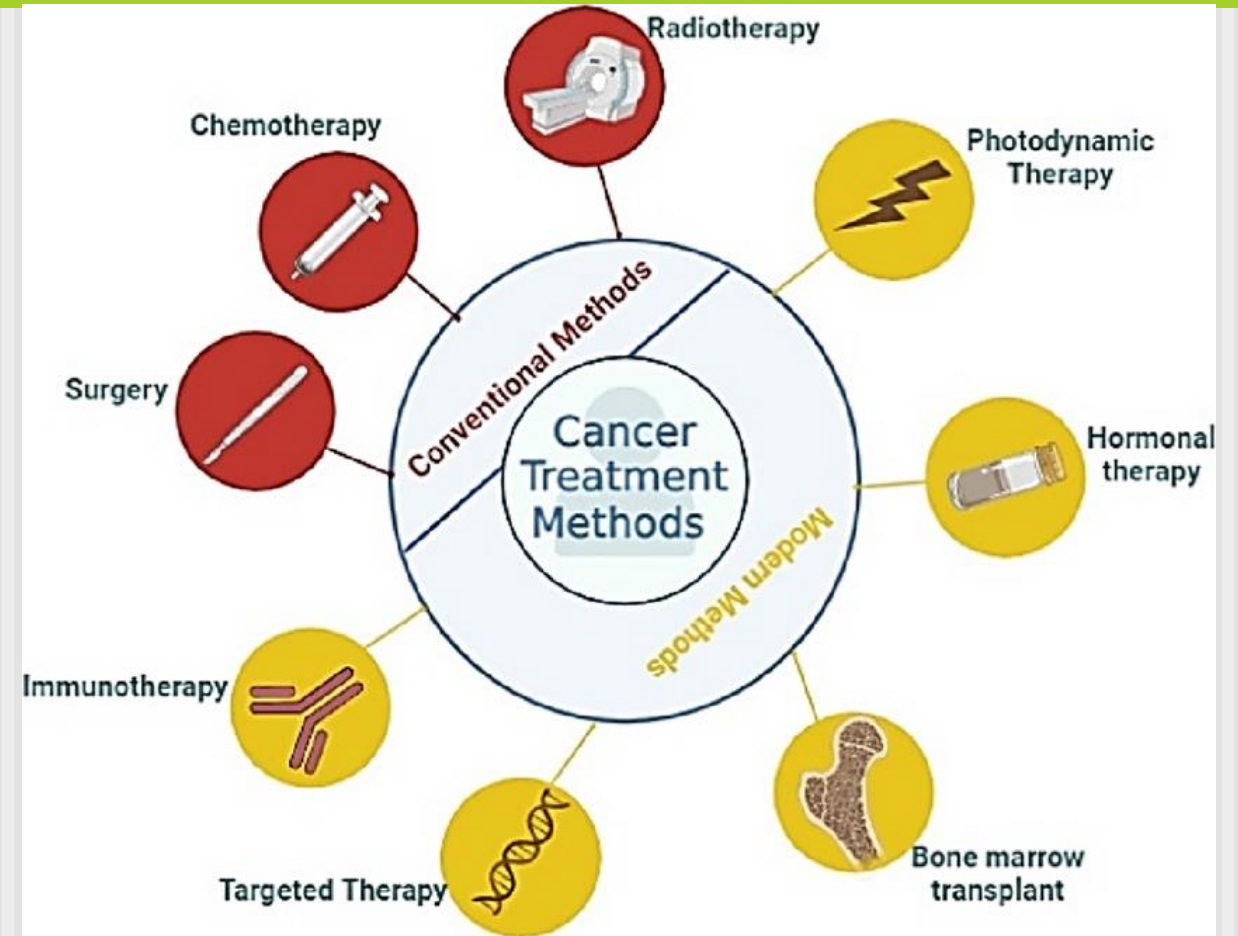
- Administered in early-stage/localized disease.
- Commonly includes surgery + adjuvant therapy.
- Objective: Eradicate all cancer → Long-term cure.
- Example: Adjuvant chemotherapy after colon or breast cancer surgery.

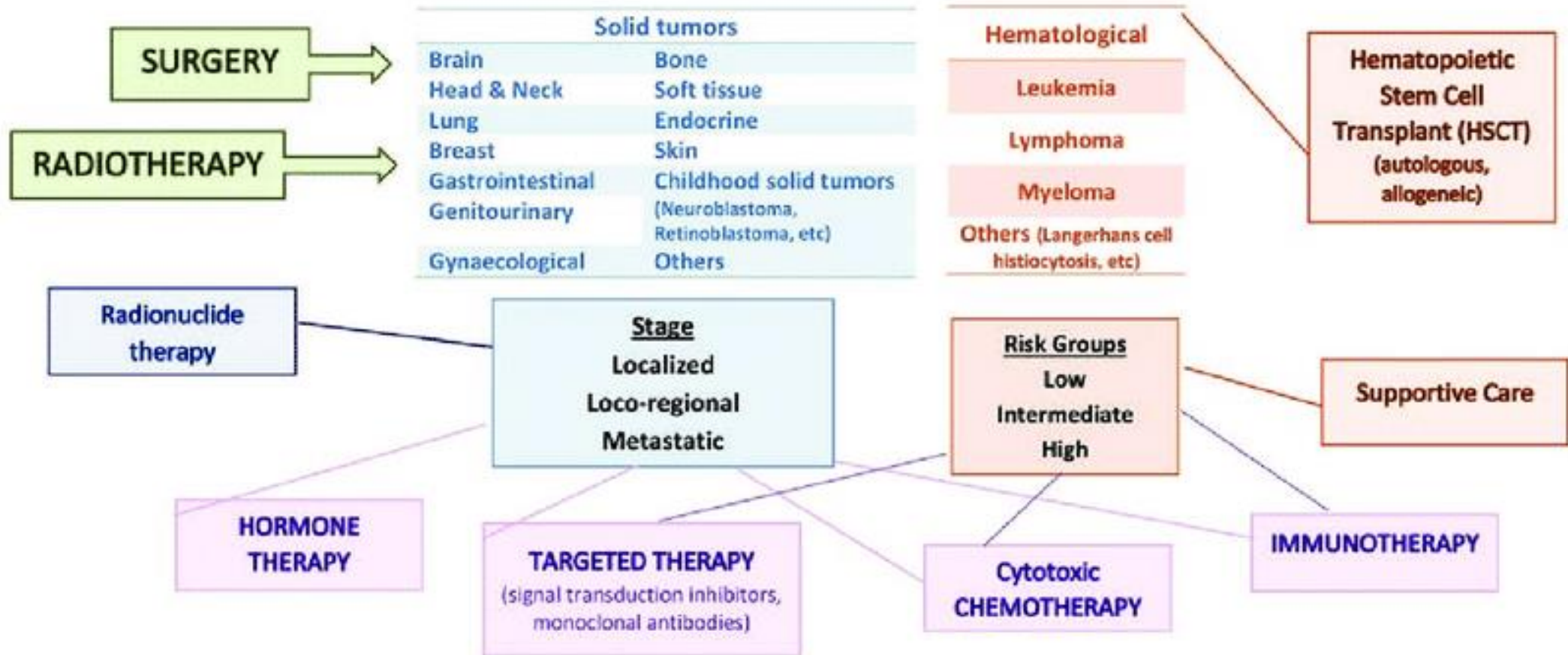
Palliative Treatment

- Given when cure is not possible (e.g., metastatic disease).
- Objectives:
 - Relieve symptoms (e.g., pain, bleeding).
 - Improve quality of life.
 - Extend survival (months to years).
- Example: Chemotherapy in metastatic pancreatic cancer.

Treatment Modalities in Cancer

- Cancer therapy comprises a wide array of treatment modalities, often used in combination to increase therapeutic efficacy.
- The choice of treatment depends on factors like cancer type, stage, genetic mutations, patient's performance status, and overall health. The major treatment modalities include:





1. Surgery

- **Surgery** is one of the oldest and most definitive treatment options for cancer.
- The goal is to physically remove the tumor from the body.
- When cancer is localized and has not spread to distant organs, surgery can be curative. For example, in early-stage breast cancer or colon cancer, complete surgical resection often leads to long-term remission or cure.
- Surgery also plays a key role in diagnosis through biopsy (removal of a tissue sample for histological examination) and staging (assessing how far cancer has spread).
- It can also be **palliative**—not to cure but to relieve symptoms such as obstruction, bleeding, or pain.
- **It can be reconstructive surgery** to restore function or appearance after major resections, such as breast reconstruction after mastectomy.
- Modern advances like laparoscopic, robotic, and minimally invasive techniques have made surgical treatments safer and more effective with reduced recovery time and complications.

Types of Cancer Surgery

1. Debulking Surgery: is mainly performed in cases where the surgeon cannot remove the entire tumor as it could damage the body.

2. Staging Surgery : is mainly done to figure out the size of the tumor and to find the extent of cancer.

3. Diagnostic Surgery: This surgery is mainly done for a biopsy which is the main way to diagnose cancer.

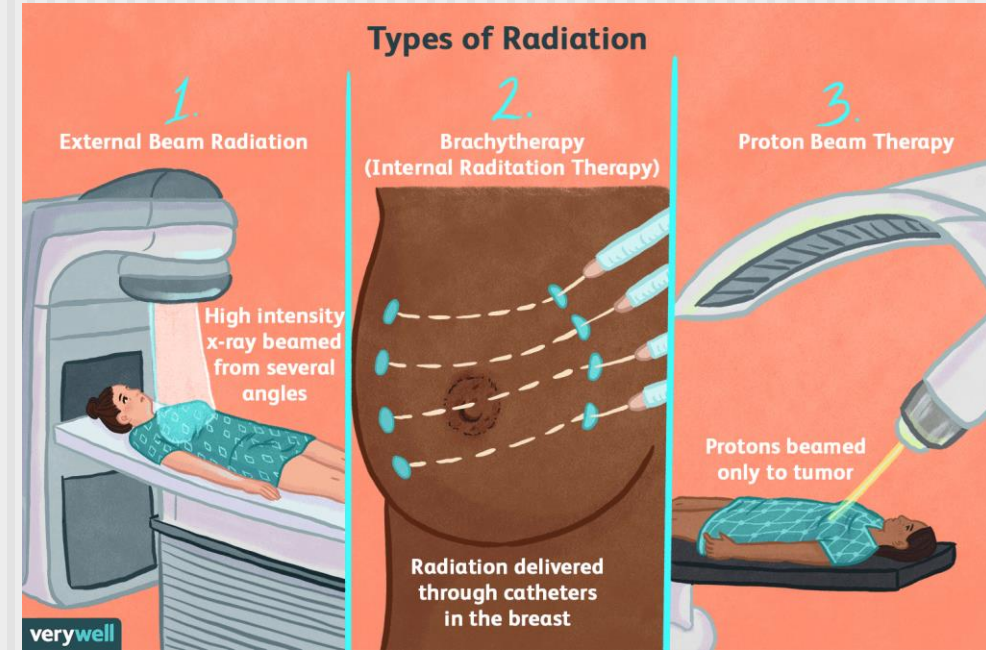


4. Palliative Surgery as the name suggests is a surgery to palliate or give relief from symptoms caused by the tumor.

2. Radiation Therapy

- Radiation therapy uses high-energy rays or particles to destroy cancer cells. It works by damaging the DNA inside cancer cells, preventing them from growing or dividing.
- Radiation therapy can be used alone for localized cancer or for cancer that may encompass a single radiation field.
- Radiation may be used as a curative treatment, often in combination with surgery or chemotherapy.
- It can also be used before surgery (neoadjuvant) to shrink tumors, or after surgery (adjuvant) to kill any remaining cancer cells.
- In advanced cases, palliative radiation can help control symptoms such as bone pain or brain metastasis.
- Side effects such as fatigue, skin irritation, mucositis, or organ-specific toxicities (like radiation pneumonitis or proctitis), which depend on the site treated.

- There are various types of radiation therapy:
 1. **External Beam Radiation Therapy (EBRT):** The most common type, where radiation is delivered from outside the body using linear accelerators.
 2. **Brachytherapy:** Radioactive materials are placed inside or near the tumor.
 3. **Systemic Radiation Therapy:** Radioactive substances are given orally or intravenously (e.g., Iodine-131 for thyroid cancer).
- This modality typically damages normal tissue surrounding the cancer, but the normal tissue typically repairs itself more readily than the cancer cells.
- Both early and late toxicities associated with radiation therapy are dependent on the organs within the radiation field.



3. Chemotherapy

- Chemotherapy refers to the use of cytotoxic drugs that kill or inhibit the growth of cancer cells.
- These drugs are particularly effective against rapidly dividing cells, which include not only cancer cells but also some normal cells like those in the bone marrow, gastrointestinal tract, and hair follicles.
- Chemotherapy is usually given in combination regimens.
- Chemotherapy may be:
 - Curative: In cancers like testicular cancer or Hodgkin lymphoma.
 - Adjuvant: After surgery to destroy microscopic residual disease.
 - Neoadjuvant: Before surgery to shrink tumors.
 - Palliative: To relieve symptoms and improve quality of life.

- There are various classes of chemotherapeutic agents:
 - **Alkylating agents** (e.g., cyclophosphamide)
 - **Antimetabolites** (e.g., methotrexate, 5-FU)
 - **Microtubule inhibitors** (e.g., paclitaxel, vincristine)
 - **Topoisomerase inhibitors** (e.g., etoposide)
 - **Anthracyclines** (e.g., doxorubicin)
- **Toxicities** include myelosuppression (low blood cell counts), mucositis, nausea, vomiting, alopecia, organ damage (like cardiotoxicity or nephrotoxicity), and secondary malignancies.

CELL CYCLE SPECIFICITY

◆ *Cell-Cycle Phase-Specific Agents:*

- Active in a particular phase of the cell cycle.
- Example: Antimetabolites act during S phase (DNA synthesis).
- Have minimal activity outside their active phase.

◆ *Cell-Cycle Phase-Non-Specific Agents:*

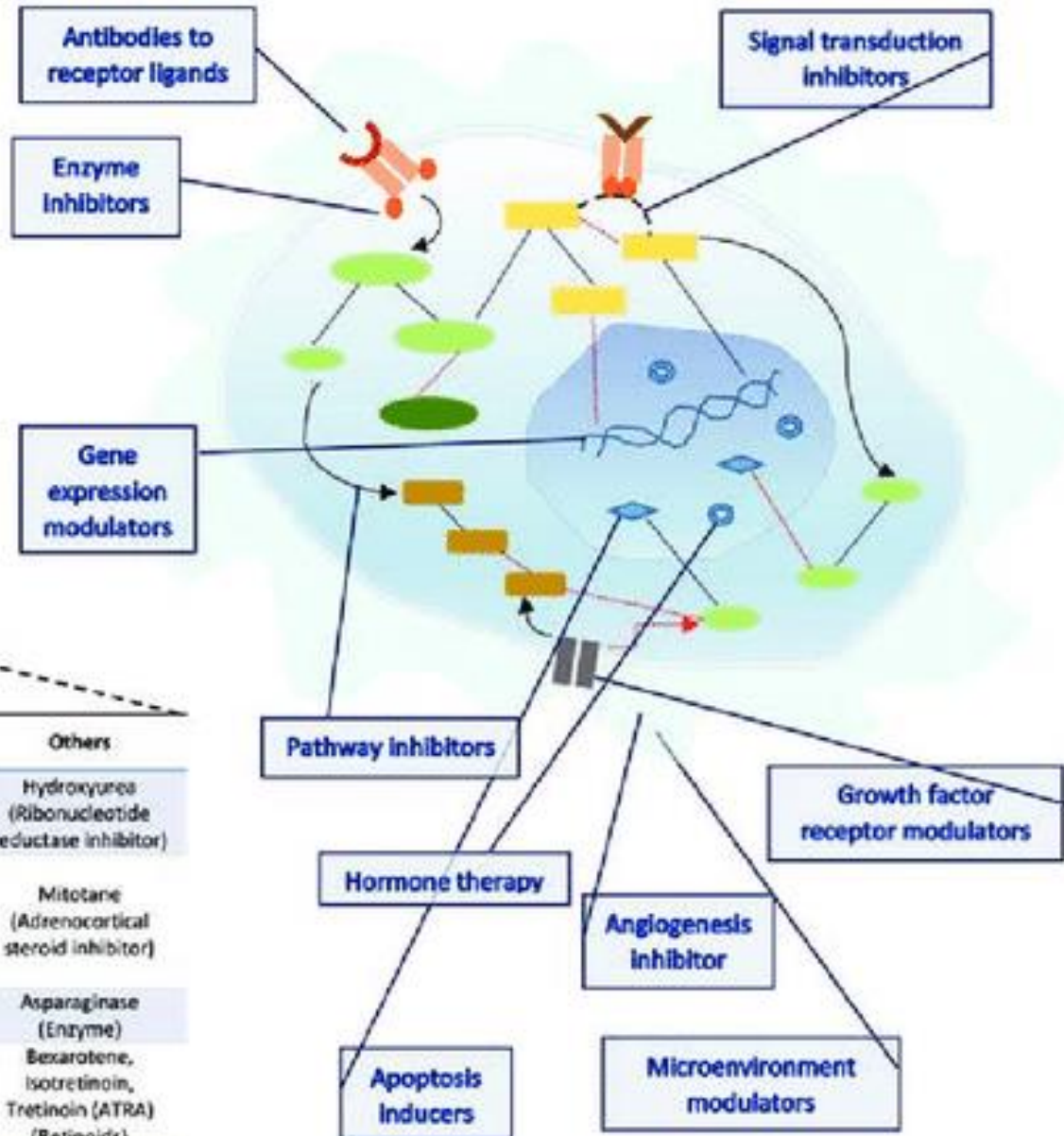
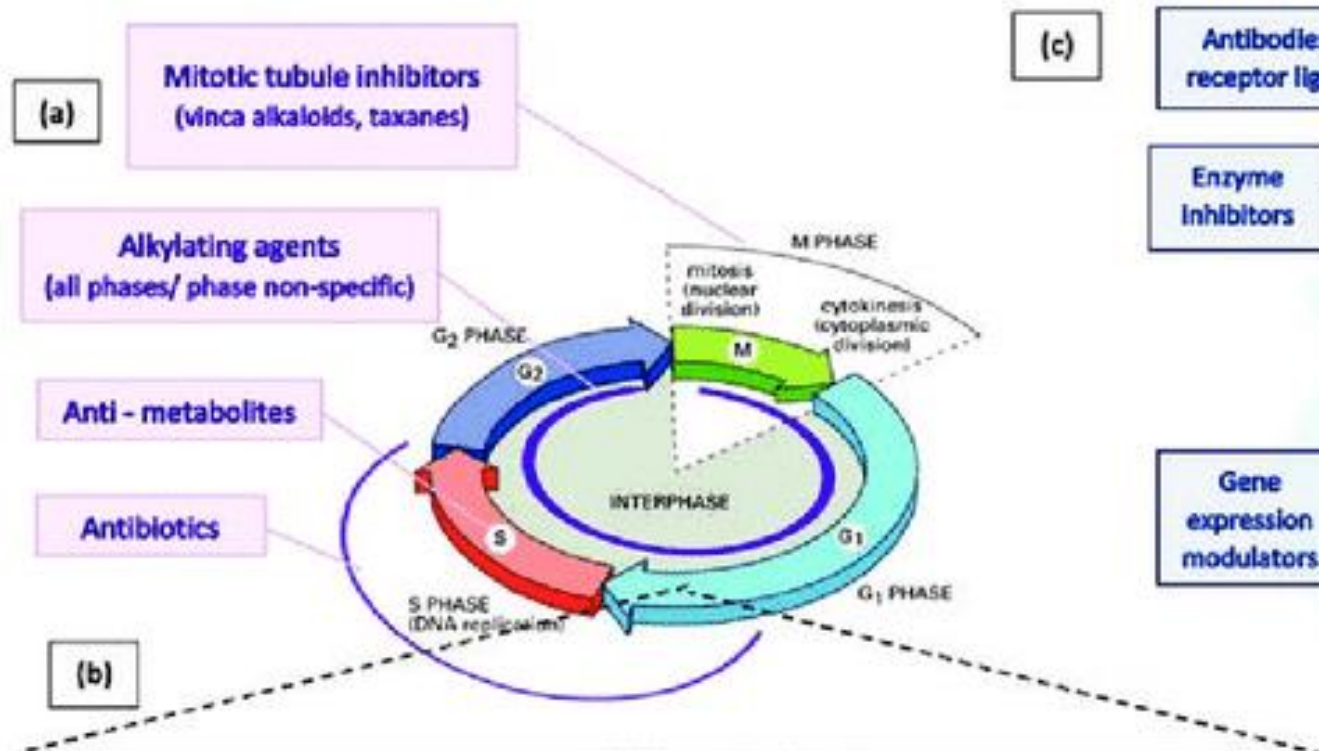
- Active in multiple phases of the cell cycle.
- Example: Alkylating agents like nitrogen mustards.
- Effective regardless of whether cells are actively dividing or not.

Chemotherapy Cycles

- Chemotherapy is given in repeating cycles.
- Cycle length allows time for:
 - Toxicity recovery (e.g., from neutropenia).
- Number of cycles depends on:
 - **Early-stage disease:** Fixed based on clinical trials.
 - **Advanced/metastatic disease:** Adjusted per individual response and tolerability.

Schedule and Dose Dependency

- ◆ ***Schedule-Dependent Agents (Phase-Specific):***
 - Require prolonged exposure (e.g., continuous infusion or repeated dosing).
 - Goal: Maximize effect during the sensitive cell cycle phase.
- ◆ ***Dose-Dependent Agents (Non-Specific):***
 - Activity is related to total dose administered.
 - Not dependent on specific timing within the cycle.
 - Schedule and Dose Dependency



Alkylating agent	Anti-metabolite	Mitotic inhibitors	Topoisomerase inhibitors	Antibiotics	Others
Nitrosoureas (Carmustine, lomustine)	Adenosine deaminase inhibitor (Fludarabine, Cladribine, Nelarabine)	Vinca Alkaloids	Topoisomerase I inhibitors	Anthracyclines	Hydroxyurea (Ribonucleotide reductase inhibitor)
Nitrogen mustards (cyclophosphamide, ifosfamide)		(Vincristine, Vinblastine, Vinorelbine,)	(Irinotecan, topotecan)	Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, Idarubicin	Mitomycin (Adrenocortical steroid inhibitor)
Busulfan	Pyrimidine antagonists (5-Fluorouracil, Cytarabine, Capecitabine, Gemcitabine)	Taxanes	Topoisomerase II inhibitors	Chromomycins	Asparaginase (Enzyme)
Melphalan		(Paclitaxel, Docetaxel, Cabazitaxel)	(Amsacrine, etoposide, teniposide)	Dactinomycin, Plicamycin	Bexarotene, Isotretinoin, Tretinoin (ATRA) (Retinoids)
Platinums (Cisplatin, Carboplatin, Oxaliplatin)	Purine antagonists (Mercaptopurine, Thioguanine,)			Miscellaneous	
Imidazole Carboxamide (Decarbazine, Procarbazine)	Anti-folates (Methotrexate, Pemetrexed)			Mitomycin, Bleomycin	

4. Hormonal (Endocrine) Therapy

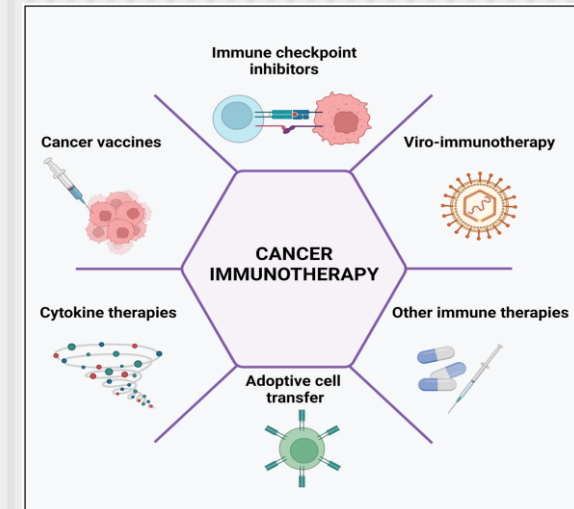
- Some cancers are hormone-sensitive, that they rely on hormones like estrogen or testosterone to grow.
- Hormonal therapy works by blocking hormone production or receptor signaling pathways. Thus, it slows or stops growth rather than killing cancer cells.
- Common uses include:
 - Breast cancer: Estrogen-receptor positive (ER+) cancers respond to agents like tamoxifen (a selective estrogen receptor modulator) or aromatase inhibitors (which lower estrogen levels).
 - Prostate cancer: Androgen deprivation therapy (ADT) via LHRH agonists (leuprolide) or anti-androgens (bicalutamide) reduces testosterone stimulation.
- Hormonal therapy is typically long-term and may be used as adjuvant therapy for years.
- Although less toxic than chemotherapy, it has side effects like hot flashes, mood changes, osteoporosis, and increased risk of cardiovascular events.

5. Targeted Therapy

- Targeted therapies are drugs designed to specifically target molecular pathways or mutations unique to cancer cells. This precision approach helps limit damage to normal cells and improves therapeutic outcomes.
- Examples include:
 - HER2 inhibitors (trastuzumab) for HER2+ breast cancer.
 - EGFR inhibitors (erlotinib) for EGFR-mutant lung cancer.
 - BCR-ABL inhibitors (imatinib) for chronic myeloid leukemia (CML).
- These therapies are based on molecular diagnostics, such as genomic sequencing or biomarker testing. They represent a major shift in cancer treatment by focusing on the underlying biology of the disease.
- Side effects depend on the specific target and drug but may include rash, diarrhea, liver dysfunction, or cardiovascular effects.

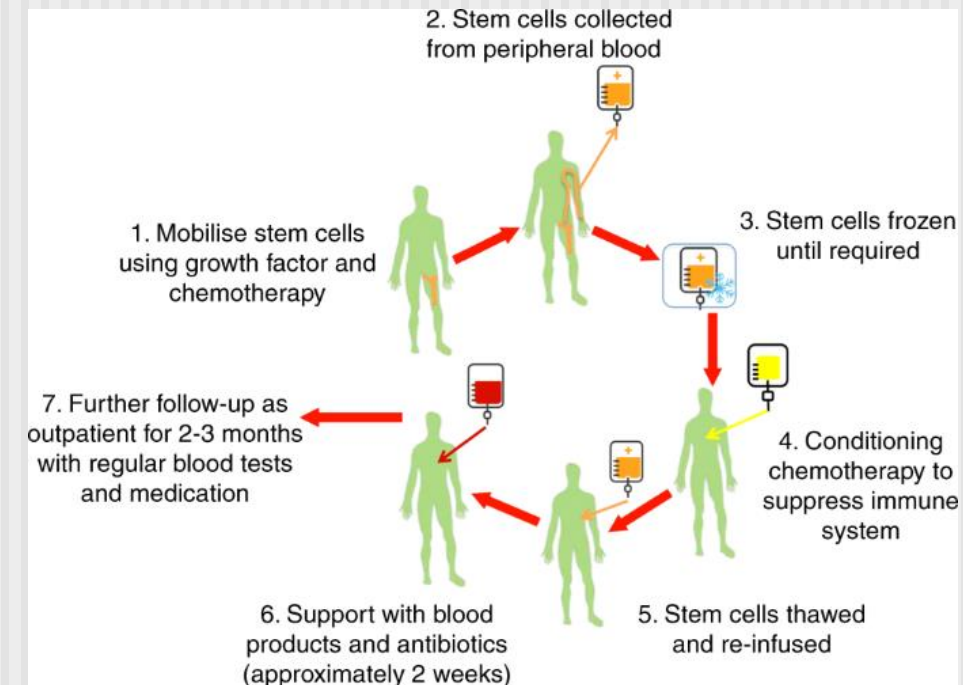
6. Immunotherapy

- Immunotherapy harnesses the body's own immune system to fight cancer. Unlike chemotherapy, which directly kills cancer cells.
- immunotherapy helps the immune system recognize and destroy them.
- Key types include:
 - **Checkpoint inhibitors:** These drugs block proteins like PD-1, PD-L1, and CTLA-4 that act as brakes on the immune system. Examples include pembrolizumab and nivolumab.
 - **CAR-T cell therapy:** Involves genetically engineering a patient's T-cells to recognize and attack cancer cells.
 - **Cytokine therapy:** Uses immune-activating proteins like interleukin-2 (IL-2).
- However, it is associated with unique toxicities called immune-related adverse events (irAEs), which can affect any organ system, most commonly the skin, gut, liver, and lungs.



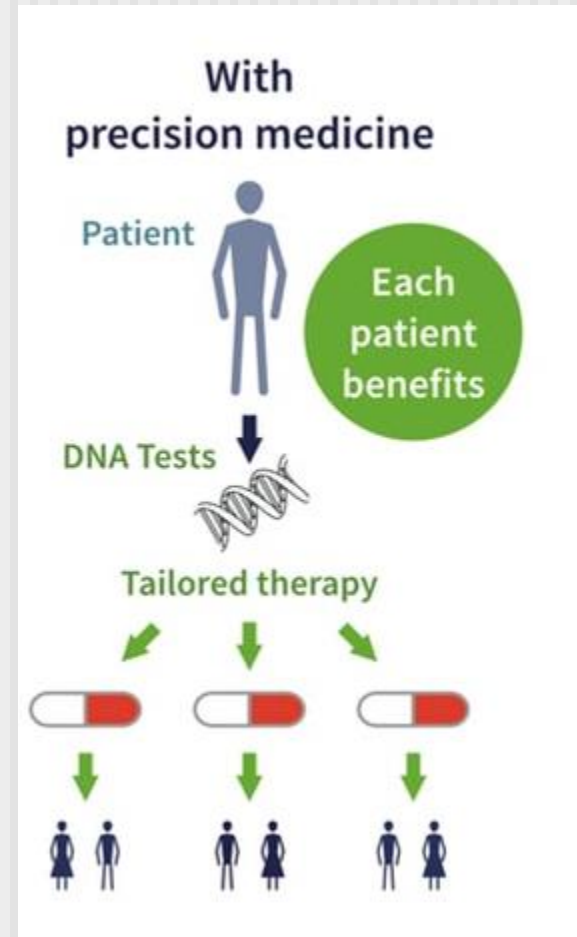
7. Hematopoietic Stem Cell Transplantation (HSCT)

- This treatment is mainly used for hematological cancers like leukemias, lymphomas, and multiple myeloma.
- It involves high-dose chemotherapy (and sometimes radiation) to eliminate cancer cells, followed by infusion of stem cells to regenerate the bone marrow.
- Types:
 - **Autologous transplantation:** The patient's own stem cells are used.
 - **Allogeneic transplantation:** Stem cells are from a donor (related or unrelated).
- HSCT allows higher doses of chemotherapy than would otherwise be tolerated. However, risks include infection, graft-versus-host disease (GVHD) in allogeneic transplants, organ toxicity, and long recovery times.



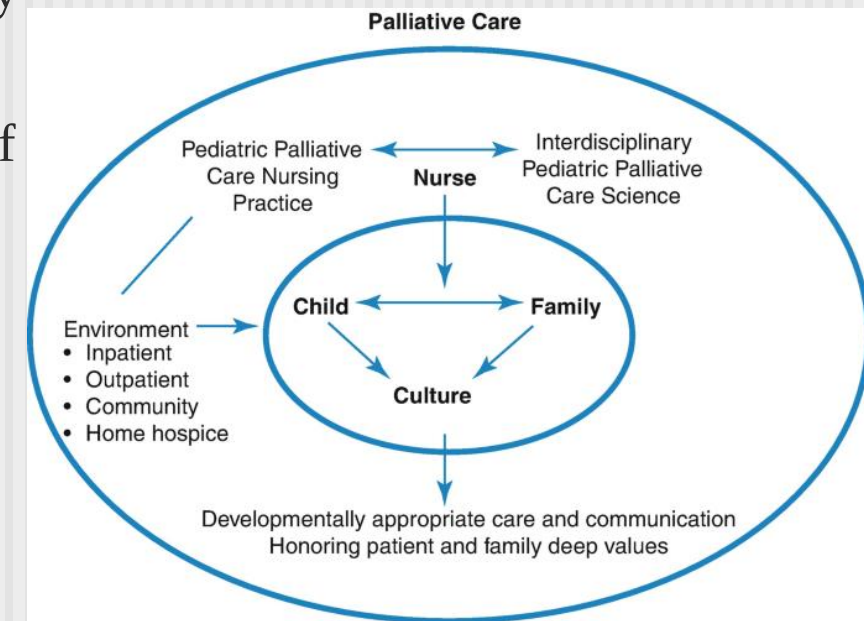
8. Precision Medicine

- Precision (or personalized) medicine in oncology means using the patient's unique genetic, molecular, and environmental profile to guide treatment decisions.
- This includes tumor genomics, pharmacogenomics, and biomarker testing.
- For instance:
 - Lung cancer patients are tested for EGFR, ALK, ROS1 mutations.
 - Breast cancer profiling (e.g., Oncotype DX) helps guide chemotherapy decisions.
- MSI-H/dMMR tumors across all cancer types may respond to pembrolizumab, regardless of the site of origin.
- The integration of genomics and bioinformatics into oncology practice is evolving rapidly.



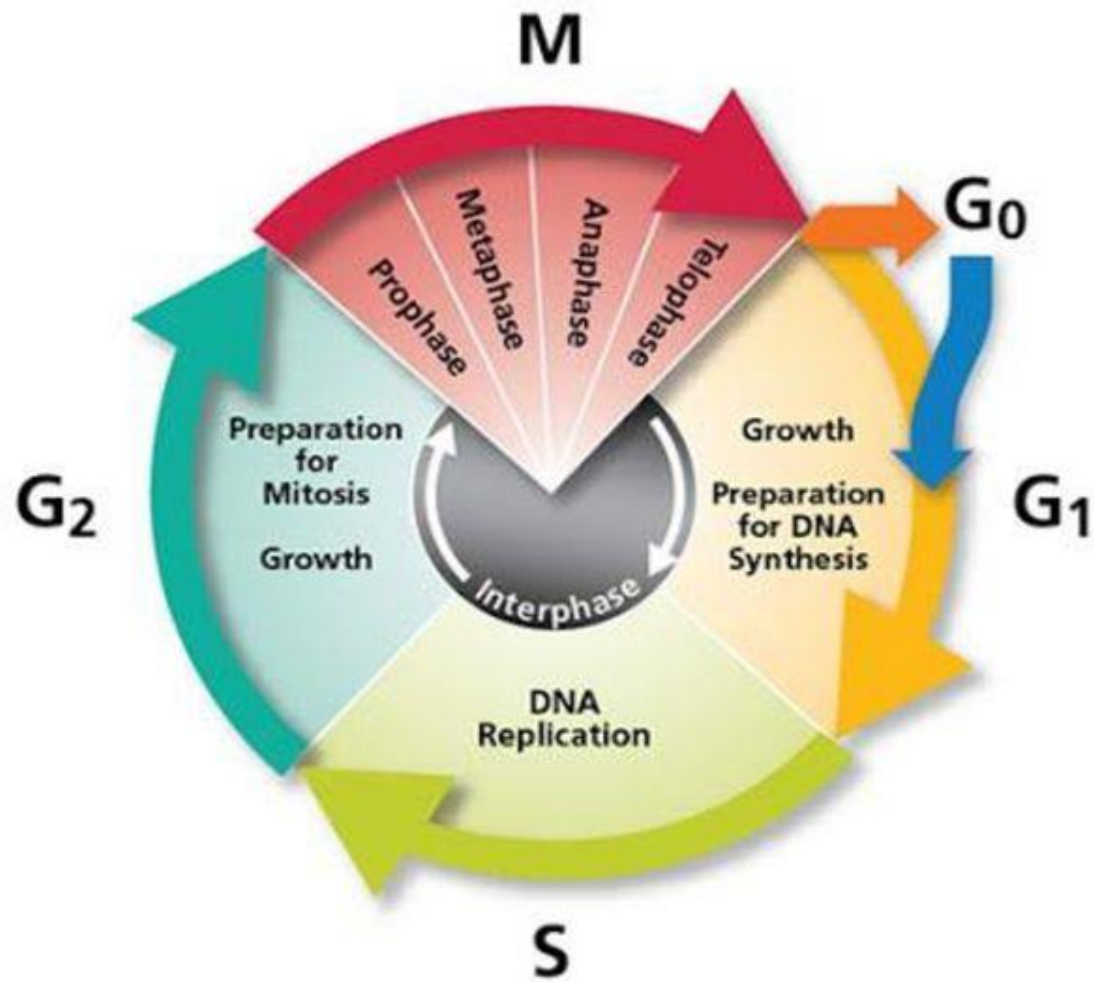
9. Palliative Care In Oncology

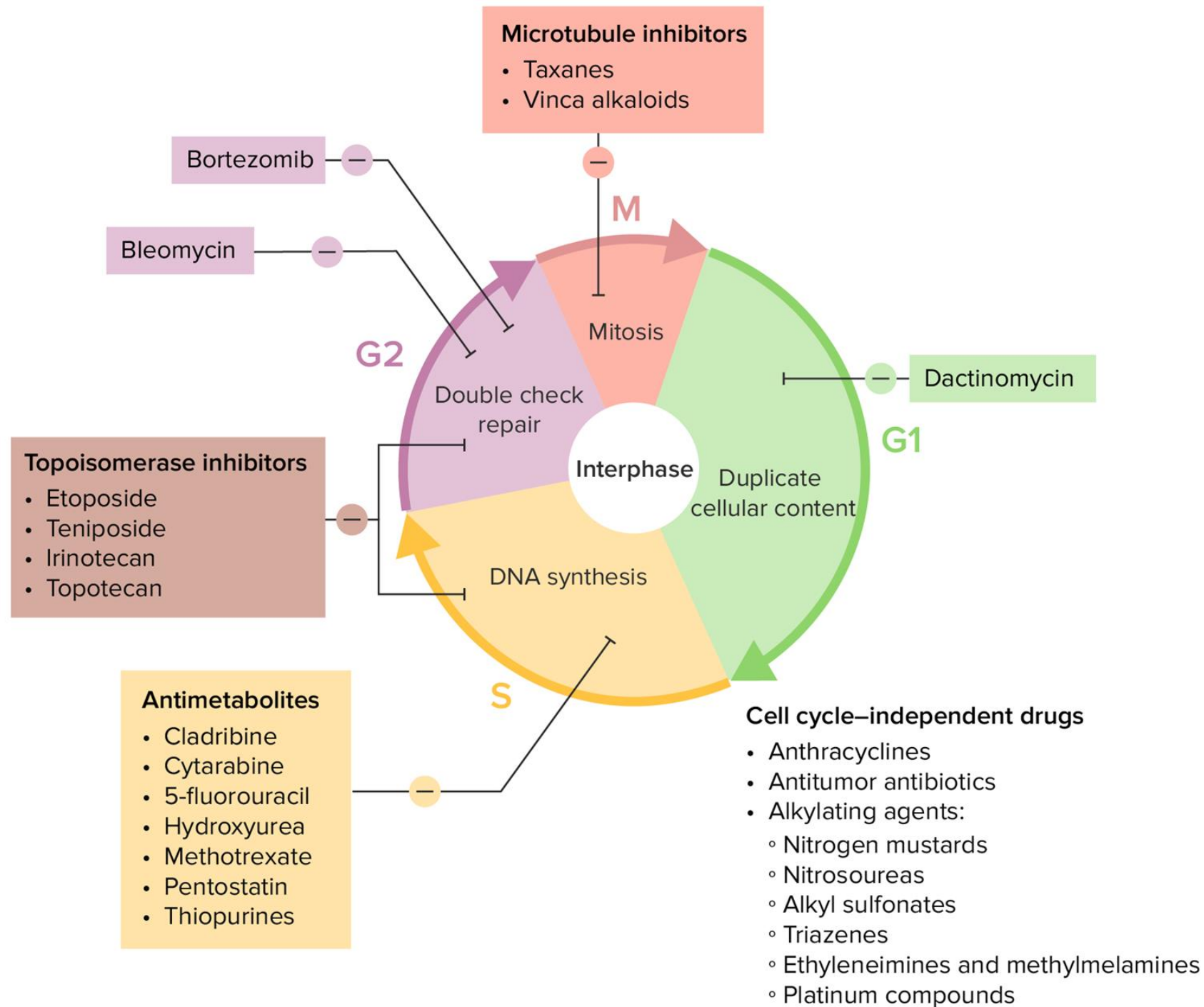
- Palliative care is often misunderstood as “end-of-life” care, but it actually aims to improve quality of life for patients at any stage of cancer.
- It focuses on symptom control, psychosocial support, and coordination of care.
- It includes:
 - Pain management
 - Management of symptoms like nausea, fatigue, dyspnea, depression, anxiety
 - Advance care planning and support for caregivers
- Palliative care can be integrated early into the cancer care plan alongside curative or life-prolonging treatments.
- It has been shown to improve outcomes, reduce hospitalizations, and even prolong survival in some studies.



- Modern cancer therapy is multimodal and multidisciplinary, involving not only oncologists but also surgeons, radiologists, pathologists, pharmacists, palliative care providers, and more.
- Understanding these treatment modalities provides a foundation for recognizing how different cancers are approached and how to personalize therapy for better outcomes.

Cell cycle





PRINCIPLES OF CANCER CHEMOTHERAPY

- Cancer chemotherapy is a systemic treatment that uses cytotoxic drugs to kill or inhibit the proliferation of cancer cells.
- These drugs aim to induce apoptosis or lethal cytotoxicity, primarily targeting DNA or metabolic sites essential for cell division and survival.
- Despite significant advances, chemotherapy faces limitations in selectivity, resistance, and toxicity.
- The following principles guide its clinical application and help design rational, effective, and patient-specific regimens.

1. Biological Basis and Selectivity Challenges
2. Requirement for Total Cell Kill
3. Tumor Heterogeneity and First-Order Kinetics of Cell Kill
4. Influence of Tumor Growth Characteristics
5. Cell Cycle Specificity of Chemotherapeutic Agents
6. Treatment Goals: Cure, Control, and Palliation

7. Types of Chemotherapy Strategies
8. Combination Chemotherapy
9. Log-Kill Hypothesis and Scheduling
10. Pharmacologic Sanctuaries
11. Drug Resistance in Chemotherapy
12. Toxicity of Chemotherapy
13. Treatment-Induced Secondary Malignancies

1. Biological Basis And Selectivity Challenges

Cancer cells are genetically and structurally similar to normal host cells, with differences such as altered cell cycle control, evasion of apoptosis, and uncontrolled proliferation.

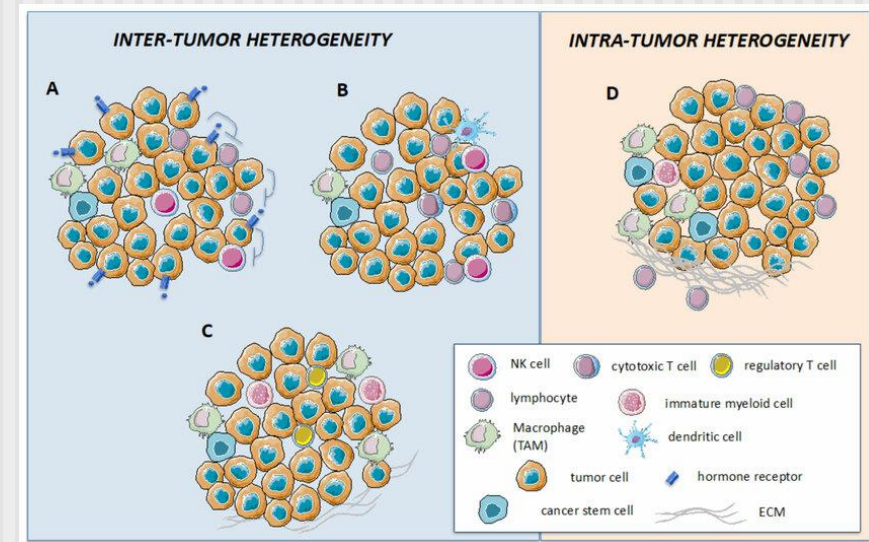
- Due to this similarity, most anticancer drugs cannot distinguish cancer cells from normal proliferating cells, leading to widespread collateral damage, especially in rapidly dividing normal tissues (bone marrow, GI mucosa, hair follicles).
- cancer cells generally evade the immune system, rendering the body's natural defence mechanisms ineffective.
- To overcome this, immunomodulatory agents like interferons, interleukin-2, and tumor necrosis factor are used as adjuvants to enhance immune-mediated cancer cell destruction.

2. Requirement For Total Cell Kill

- A fundamental principle of chemotherapy is the need to eradicate every malignant cell to achieve a true cure.
- A single surviving carcinogenic cell can potentially repopulate and cause disease relapse.
- Therefore, survival after chemotherapy is inversely related to the number of residual malignant cells.
- This principle underscores the importance of early, aggressive, and comprehensive therapy aimed at complete remission, rather than mere symptom control or partial response.

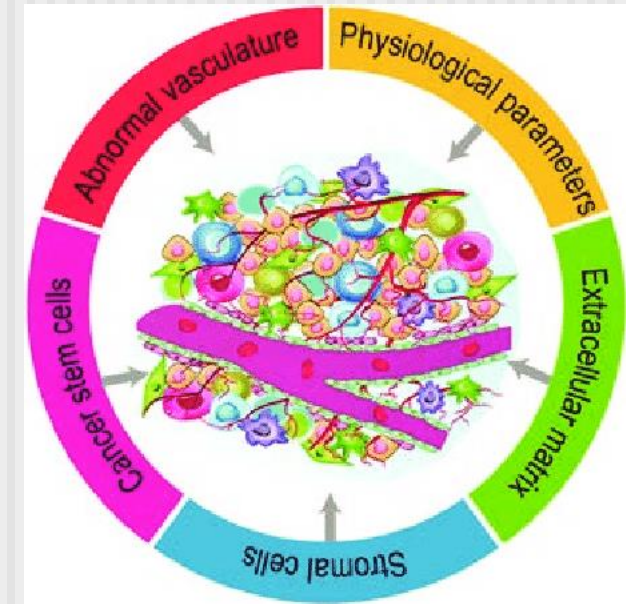
3. Tumour Heterogeneity And First-order Kinetics Of Cell Kill

- Cancer cell populations are heterogeneous.
- They include subpopulations with varying proliferative rates and drug sensitivities.
- Chemotherapeutic agents typically kill a constant proportion of cancer cells with each dose—this is known as first-order kinetics or the "log-kill hypothesis."
- Repeated cycles are therefore essential to achieve cumulative cytoreduction and ultimately eliminate all cancer cells.
- The concept also emphasizes the value of combining chemotherapy with surgery or radiation, especially to treat residual microscopic disease.



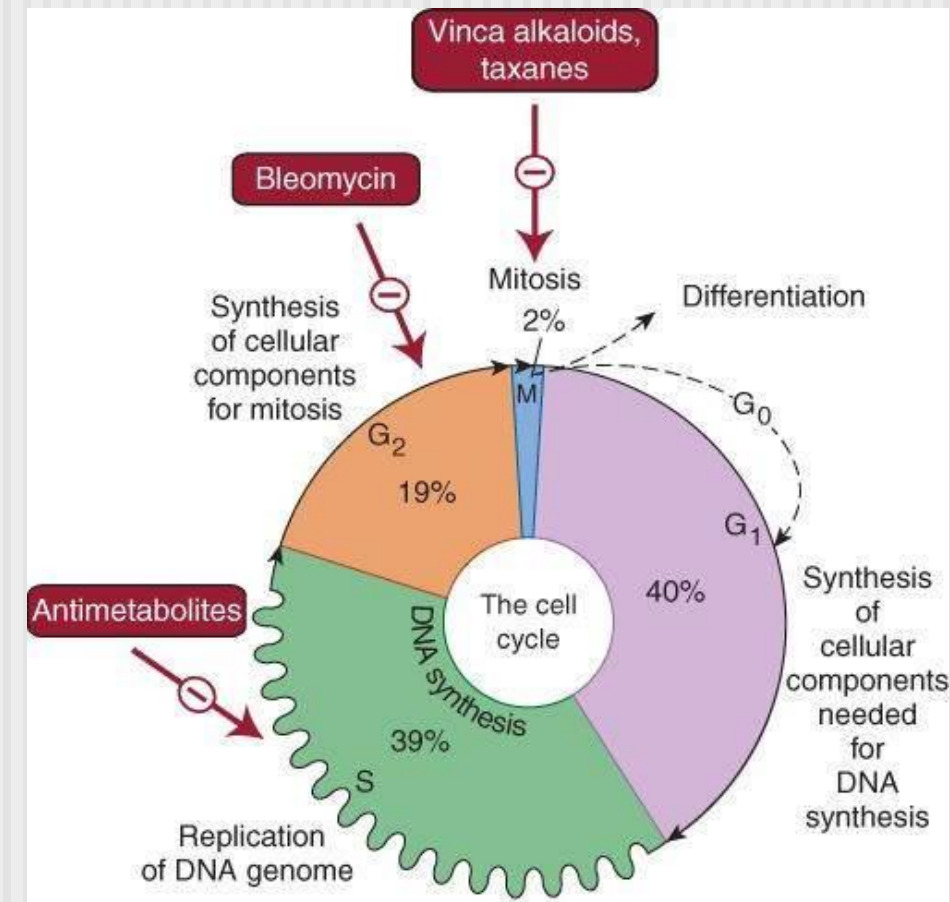
4. Influence Of Tumour Growth Characteristics

- Tumour cell sensitivity to chemotherapy is influenced by the proportion of cells actively dividing.
- Rapidly dividing tumours (e.g., leukaemia's) are more sensitive to chemotherapy than slow-growing tumours (e.g., colon carcinoma).
- Moreover, tumour growth is not linear—it slows as tumours enlarge due to reduced blood supply, oxygen, and nutrient availability.
- This explains why chemotherapy is often more effective after debulking a large tumour with surgery or radiation.



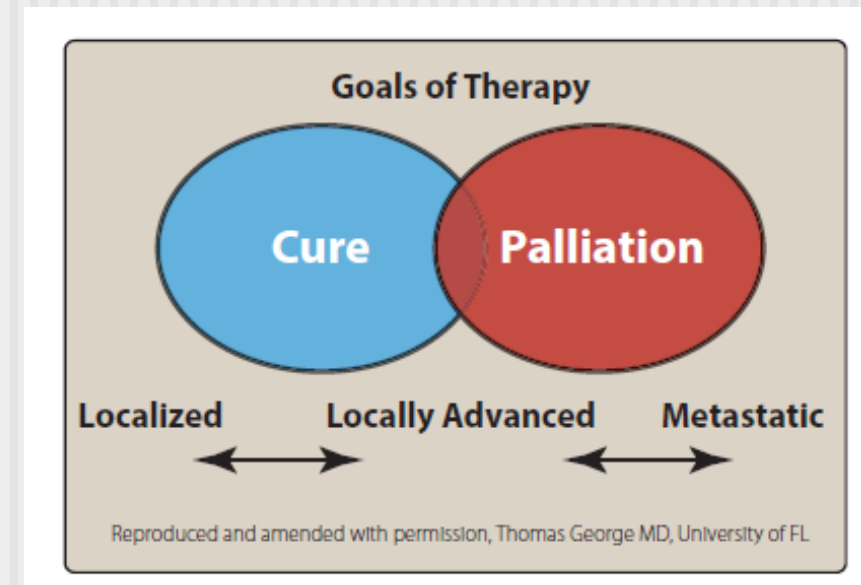
5. Cell Cycle Specificity Of Chemotherapeutic Agent

- Chemotherapeutic drugs can be classified as:
 - Cell cycle-specific agents (CCS):** Active only against dividing cells (e.g., antimetabolites like methotrexate, vinca alkaloids).
 - Cell cycle-nonspecific agents (CCNS):** Effective against both dividing and resting cells (e.g., alkylating agents, anthracyclines).
- Combining CCS and CCNS drugs provides broader cytotoxic coverage and maximizes tumour kill.
- Understanding the timing of drug administration based on cell cycle phases enhances treatment efficacy ("kinetic scheduling").



6. Treatment Goals: Cure, Control, And Palliation

- The goals of chemotherapy vary based on cancer type, stage, and response to therapy:
 - **Curative therapy:** Achieving long-term, disease-free survival by eliminating all malignant cells (e.g., in testicular cancer, pediatric ALL).
 - **Control (chronic treatment):** Preventing cancer progression and maintaining quality of life when cure is not possible.
 - **Palliation:** Reducing symptoms, minimizing complications, and improving quality of life in advanced stages, even without prolonging survival.
- These goals are dynamic and may evolve during the course of the disease.



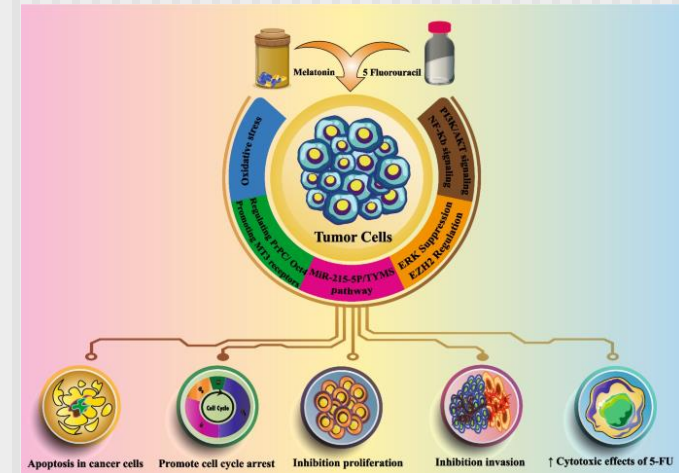
7. Types Of Chemotherapy Strategies

- **Adjuvant chemotherapy:** Administered after surgery or radiation to target micro metastases.
- **Neoadjuvant chemotherapy:** Given before surgery to reduce tumour size and improve respectability.
- **Maintenance chemotherapy:** Low-dose, long-term therapy aimed at sustaining remission.
- **Induction and consolidation therapy:** Terms used in haematological malignancies to refer to initial intense therapy followed by additional cycles to eliminate residual disease.



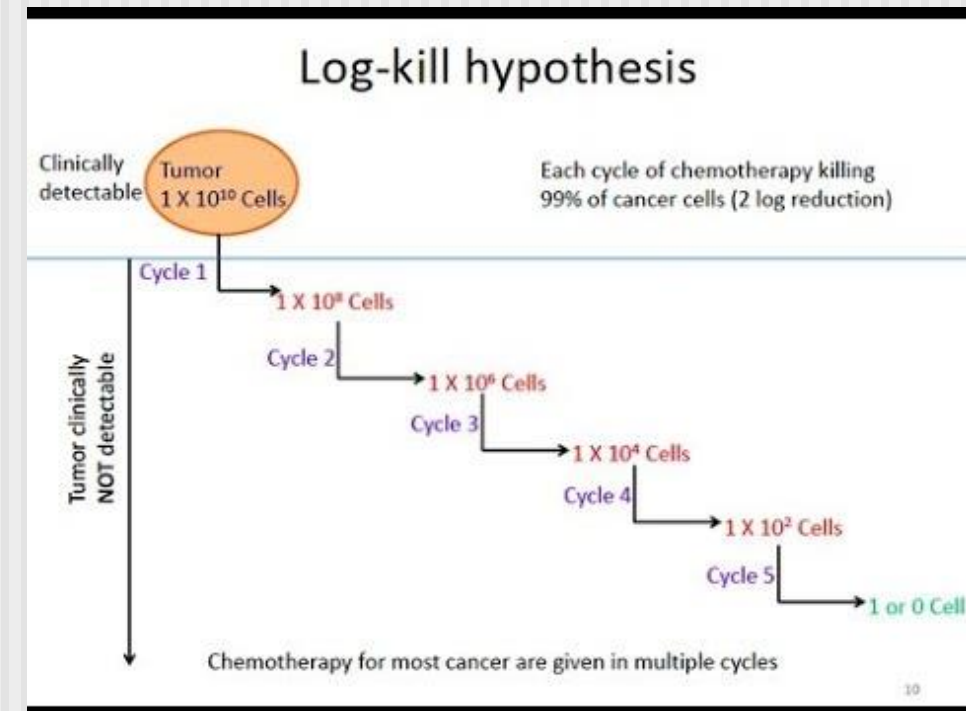
8. Combination Chemotherapy

- Modern cancer treatment employs combinations of 2–5 drugs to maximize tumour cell kill and prevent resistance.
- Effective combinations are designed based on:
 1. Drugs with activity as monotherapy
 2. Different mechanisms of action
 3. Non-overlapping toxicities
 4. Different mechanisms of resistance
 5. Synergistic or additive interactions
 6. Cell cycle considerations
- Examples include:
 - R-CHOP (for non-Hodgkin lymphoma): Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone
 - ABVD (for Hodgkin lymphoma): Adriamycin + Bleomycin + Vinblastine + Dacarbazine
- Drug regimens are typically administered in cycles to allow normal tissue recovery.



9. Log-kill Hypothesis And Scheduling

- Chemotherapy effectiveness is governed by the "log-kill" model.
- A 1-log kill reduces tumour burden by 90%, while a 5-log kill reduces 100,000-fold.
- Unlike infections, where the immune system can clear residual pathogens, cancer requires continued treatment to eliminate all tumour cells.
- This principle justifies:
 - Repeated cycles of chemotherapy
 - Use of adjuvant therapy even when no visible tumor remains
- Drug doses are commonly calculated using body surface area (BSA) to personalize treatment.

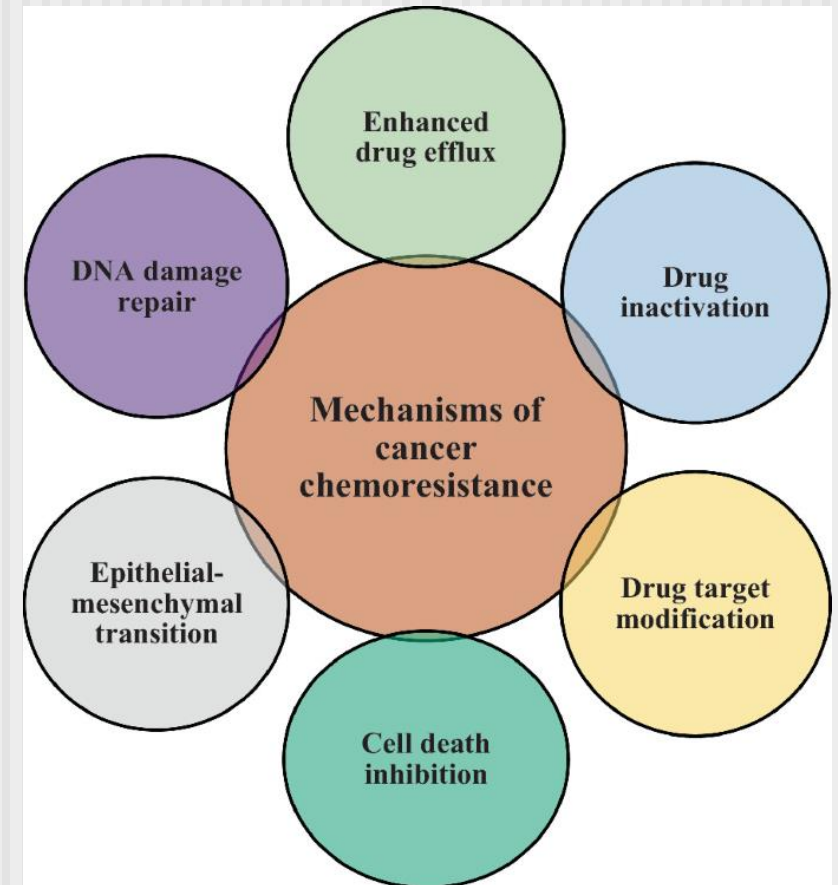


10. Pharmacologic Sanctuaries

- Some body sites act as "sanctuaries" where standard chemotherapy cannot penetrate effectively, such as the central nervous system (CNS) and testicles.
- Leukemic cells in the CNS, for example, may require:
 - **Intrathecal chemotherapy** (e.g., methotrexate)
 - **Craniospinal radiation**
- Similarly, poorly vascularized tumour cores may be inaccessible to drugs, limiting treatment success.

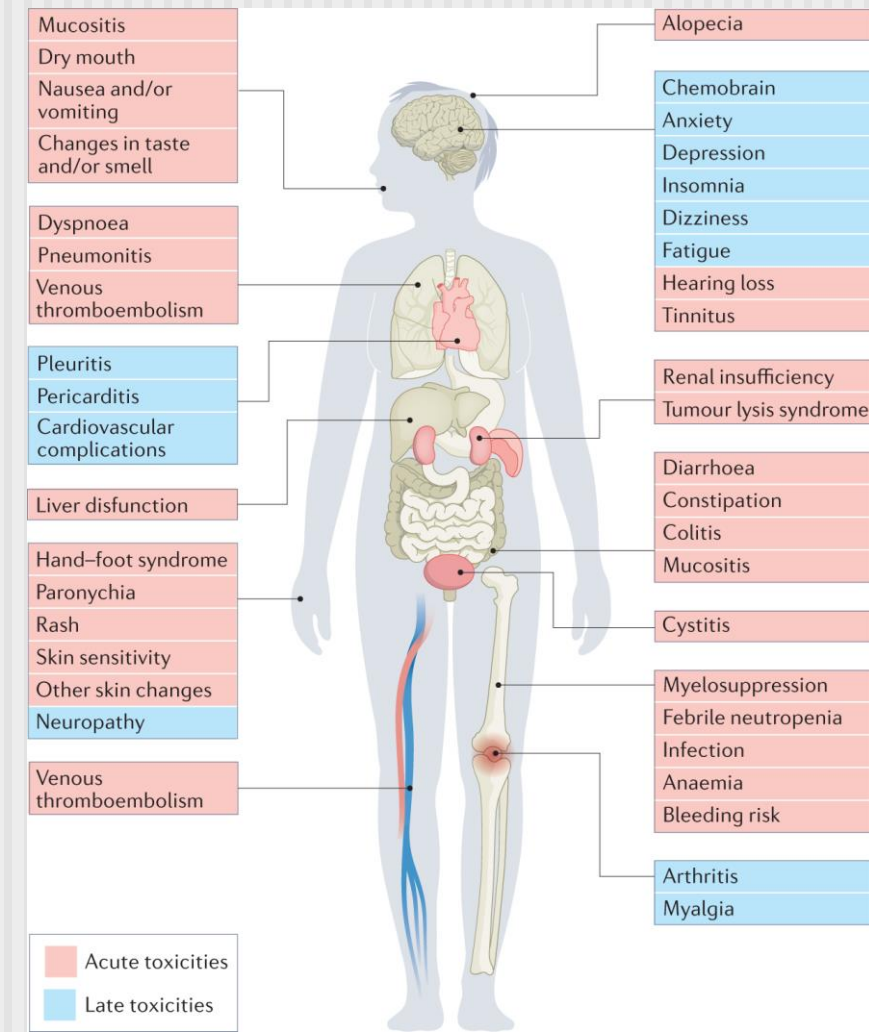
11. Drug Resistance In Chemotherapy

- Resistance can be:
 - Intrinsic (primary):** Seen in tumours like melanoma, where cells are naturally unresponsive.
 - Acquired:** Develops over time due to mutations, particularly with monotherapy or subtherapeutic dosing.
 - Multidrug resistance (MDR)** is mediated by efflux pumps like **P-glycoprotein**, which actively transport drugs out of cells.
 - This leads to cross-resistance to structurally unrelated agents.
 - Inhibitors of P-glycoprotein (e.g., verapamil) have limited clinical use due to toxicity, but research into safer alternatives continues.



12. Toxicity Of Chemotherapy

- Since chemotherapeutic agents target dividing cells, rapidly proliferating normal cells are also affected.
- Common side effects include:
 - **Myelosuppression:** Risk of infections, anemia, and bleeding
 - **Gastrointestinal toxicity:** Nausea, vomiting, mucositis, diarrhea
 - **Alopecia:** Hair loss
 - **Organ-specific toxicities:**
 - Cyclophosphamide → Hemorrhagic cystitis
 - Doxorubicin → Cardiotoxicity
 - Bleomycin → Pulmonary fibrosis
- Some effects are reversible (e.g., alopecia), while others may be permanent (e.g., cardiac damage).
- **Strategies to reduce toxicity include:**
 - Use of cytoprotective agents (e.g., mesna for cyclophosphamide)
 - Leucovorin rescue after high-dose methotrexate
 - Growth factor support (e.g., G-CSF)
 - Autologous bone marrow rescue



13. Treatment-induced Secondary Malignancies

- Ironically, some chemotherapeutic agents are mutagenic and can lead to secondary cancers, especially after long-term use of alkylating agents or topoisomerase inhibitors.
- These treatment-induced cancers, such as therapy-related acute myeloid leukemia, typically appear years after initial therapy.

