بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

FINAL | Lecture #4

Chemotherapy for Leukemia and Lymphoma (Pt. 1)

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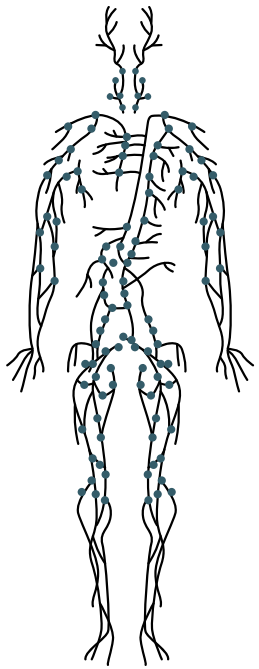


Tumor Biology

- Cancer is a genetic disease that results from the accumulation of mutations that:

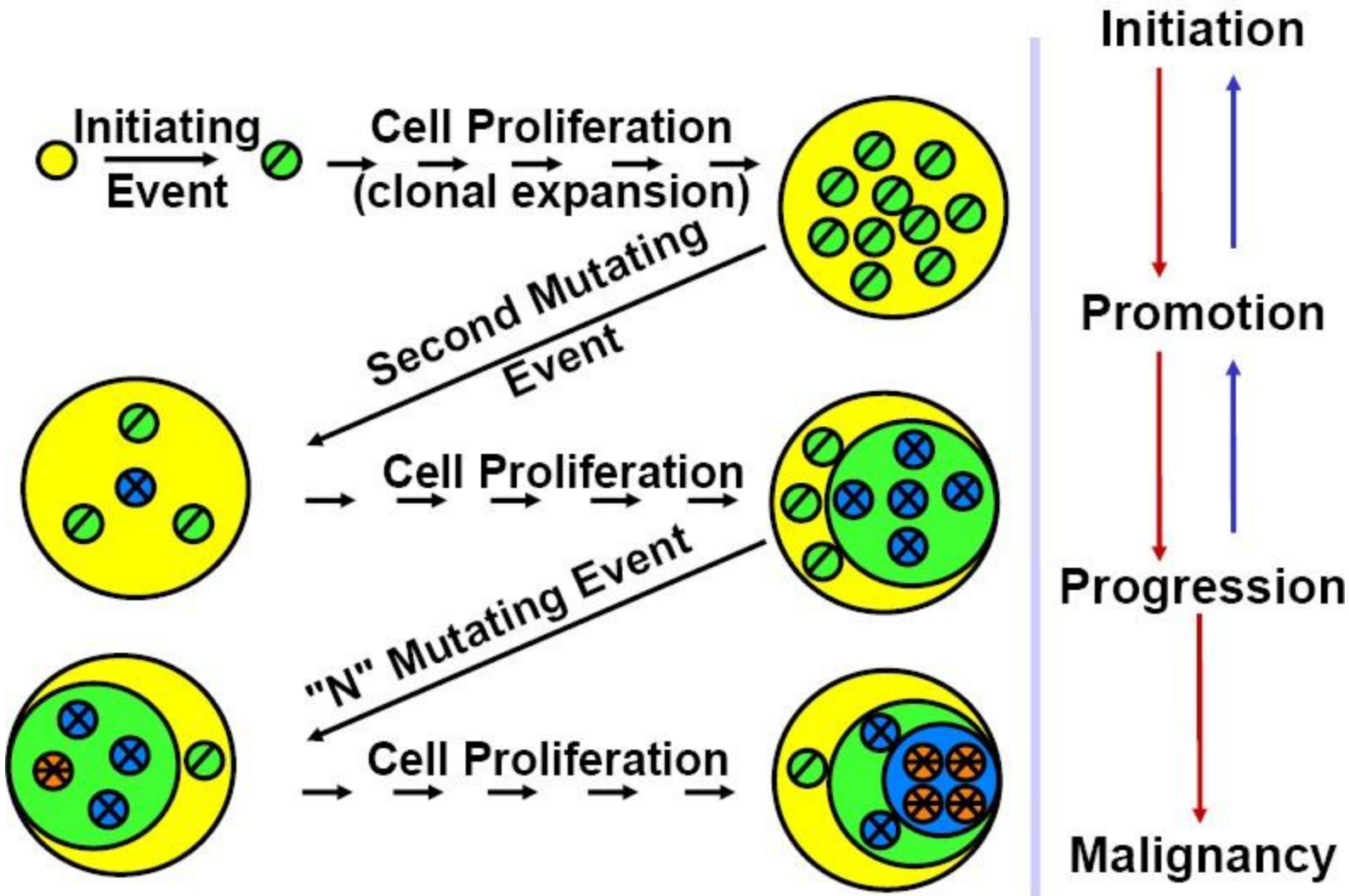
1. Activate dominant oncogenes in the growth proliferative pathways send false positive signals that constitutively drive the proliferative cycle.
2. Inactivate tumor suppressor genes which function in various biochemical processes.

- In cancer, the main problem is its **monoclonal origin**, meaning it starts from a **single transformed cell**. In **liquid tumors**, such as **lymphomas** or **leukemias**, these malignant cells circulate in the **blood or lymph**, while in **solid tumors**, they remain **confined within tissues**.
- The challenge in **cancer treatment** is to **eliminate all malignant cells**, because even a **single surviving cell** can **divide and cause tumor recurrence**.

Tumor Biology

3. Damage is also done to DNA repair genes so that, over time, giving rise to hypermutability and tumor heterogeneity.
   - The outcome is that tumor cells relentlessly drive through the proliferative cell cycle and generally lose the capacity to differentiate.
4. To become malignant:
   A. The mutated cells have to acquire the capacity to avoid immune detection to metastasize.
   B. Be able to induce angiogenesis in order to provide themselves with a blood supply.

Stages of Carcinogenesis

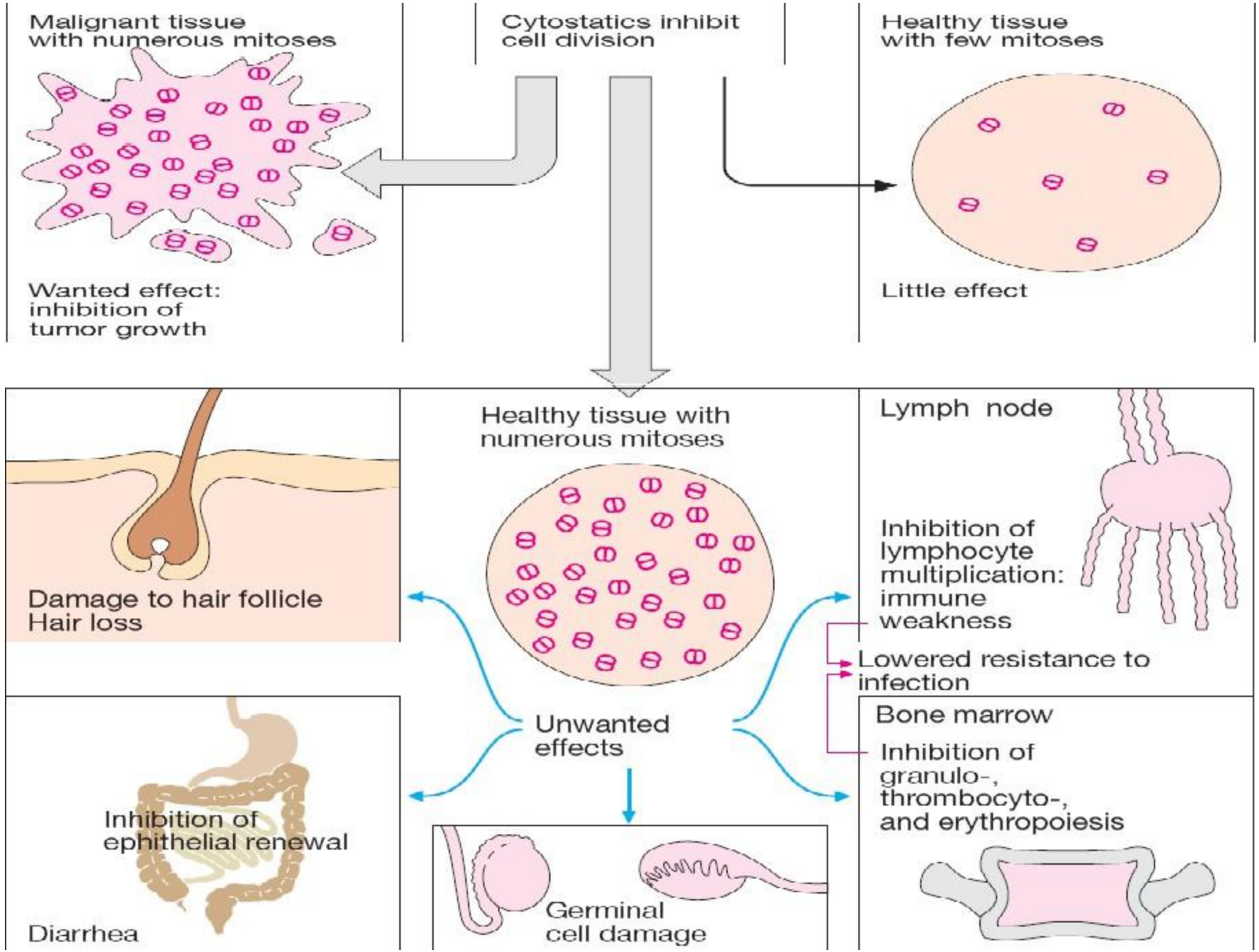


Molecular Stages in the Development of Cancer (Carcinogenesis)

- Although the **exact trigger** of a cancer's **monoclonal origin** may vary, we know that **genetic mutations** caused by **environmental, chemical, or genetic factors** can initiate the process.
- To understand how cancer begins, we describe several stages:
  1. **Initiation:** The **first genetic mutation** occurs in a normal cell, transforming it into a **potentially malignant cell**.
  2. **Promotion:** The mutated cell **proliferates abnormally**, losing normal **growth control** and forming a **clonal population**.
     (The change from yellow to green color in the illustration represents the first mutation.)
  3. **Progression:** Additional **mutations accumulate**, producing cells with **increasingly aggressive behavior** and leading toward **malignancy**.
  4. **Malignancy:** The tumor becomes **heterogeneous**, with cells that show **reduced immunogenicity** and a high **mutation rate**. These continuously changing cells make **treatment more difficult**, as they can **adapt and resist therapy over time**.

Cancer Chemotherapy

- Cancer drugs are not specific for cancer cells but are cytotoxic to all proliferating cells in cycle.
- Their major unwanted toxicity is damage to bone marrow function and to the epithelial lining of the gut.
- Generally speaking, these are the dose-limiting toxicities.
- After treatment, **immunotherapy** may be used to **enhance the patient's immune response**, helping the body **target residual cancer cells**. However, **chemotherapy and radiotherapy** often damage **rapidly dividing healthy cells**, causing **bone marrow suppression**, which can sometimes lead to severe complications or death.
- **Solid tumors** are generally **harder to cure** because the **dense mass of cancer cells** creates a **hypoxic core** due to poor blood circulation. This low-oxygen environment **forces tumor cells to adapt**, entering a **G_0 (resting) phase**.
  - The **G_0 phase**, also known as the **resting phase**, is a **non-dividing state** in the cell cycle where cells remain **quiescent**, either **temporarily or permanently**.

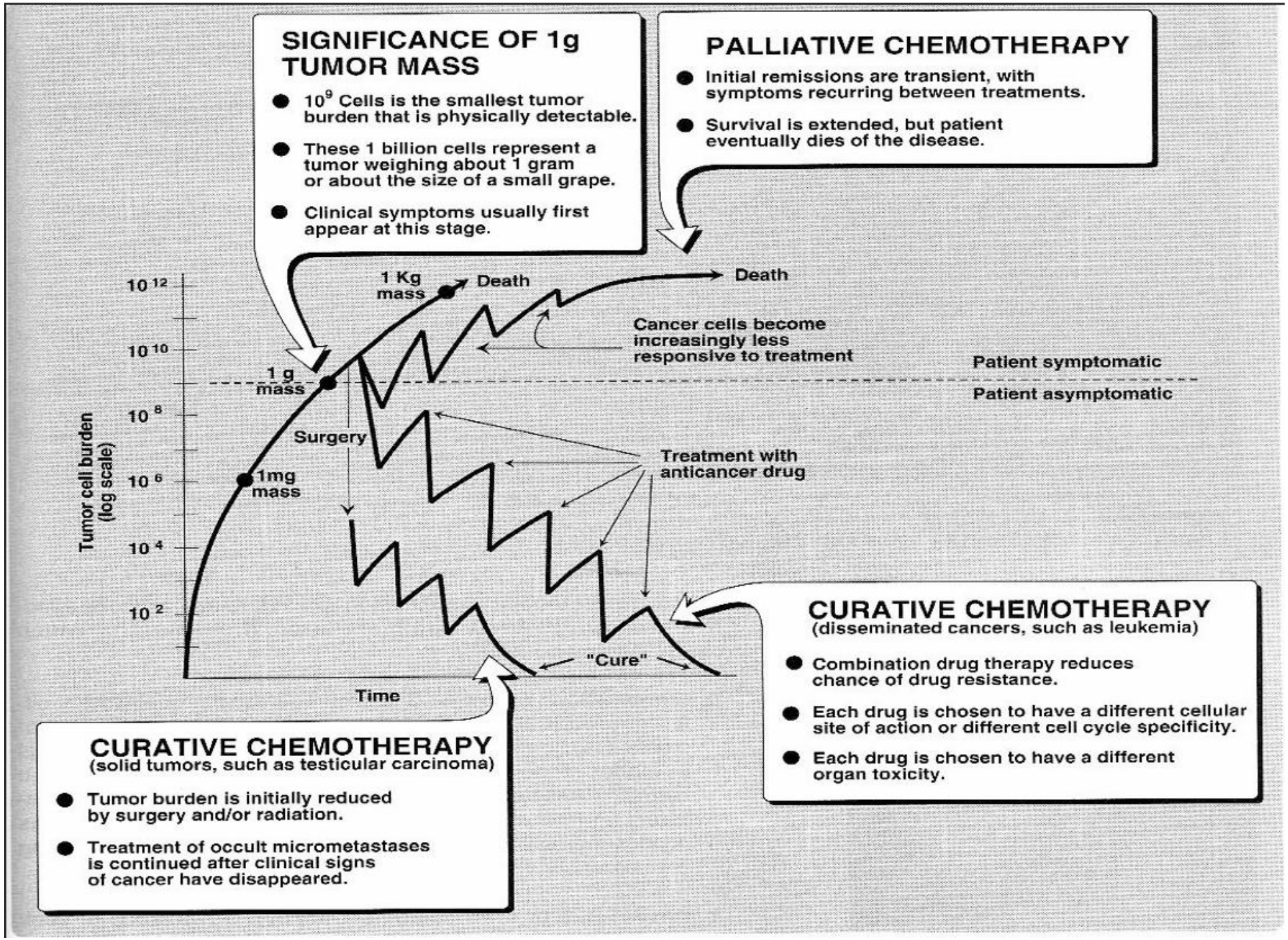

Malignant tissue with numerous mitoses
Cytostatics inhibit cell division
Healthy tissue with few mitoses
Wanted effect: inhibition of tumor growth
Little effect
Healthy tissue with numerous mitoses
Damage to hair follicle
Hair loss
Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered resistance to infection
Unwanted effects
Bone marrow
Inhibition of granulo-, thrombocyto-, and erythropoiesis
Inhibition of ephithelial renewal
Diarrhea
Germinal cell damage

Cytotoxic Effects and Complications of Chemotherapy

- **Chemotherapy** consists of **potent cytotoxic drugs** that **destroy rapidly dividing cells**, including **healthy proliferating cells**.
- The **main side effects** result from this non-selective action and include:
  - **Alopecia:** due to the destruction of hair follicle cells.
  - **Gastrointestinal ulcers:** caused by inhibition of **GIT epithelial cell renewal**.
  - **Leukopenia:** inhibition of **granulocyte and lymphocyte production**, leading to **immune suppression** and **increased infection risk**.
  - **Thrombocytopenia:** reduced platelet production, resulting in a **high risk of bleeding**.
  - **Anemia (cytopenia):** due to **suppressed erythropoiesis**.
  - **Infertility:** caused by the **destruction of germinal cells**.
- These effects leave the patient **immunocompromised**, making them vulnerable to **opportunistic bacterial, viral, and fungal infections**. Therefore, **patients must be monitored closely**, as even a **slight fever can indicate a life-threatening infection**.

Chemotherapy Resistance and Ethical Challenges

- **Non-proliferating cells** are **largely unaffected by chemotherapy**, since these drugs primarily target **rapidly dividing cells**.
- While **cancer cells** are intended targets, **normal proliferating cells** are often **damaged more severely**, as **mutations in genes such as p53, KRAS, BRAF, or overexpression of the epidermal growth factor receptor (EGFR)** can make **tumor cells resistant** to treatment. Over time, these mutations may cause cancer cells to **stop responding to therapy**.
- **Chemotherapy** aims to **eliminate all malignant cells**, because the **immune system** is often unable to effectively destroy even a **single surviving cancer cell**, unlike its efficient response against **bacteria or foreign antigens**.
- Some patients choose **palliative care** to focus on **comfort and quality of life**, accepting a dignified end rather than enduring aggressive treatments.
- Others may **relapse** with a **more aggressive cancer** after therapy, while some **cannot afford treatment**, raising **ethical concerns** about access to care and treatment decisions.


SIGNIFICANCE OF 1g TUMOR MASS
10^9 Cells is the smallest tumor burden that is physically detectable.
These 1 billion cells represent a tumor weighing about 1 gram or about the size of a small grape.
Clinical symptoms usually first appear at this stage.
PALLIATIVE CHEMOTHERAPY
Initial remissions are transient, with symptoms recurring between treatments.
Survival is extended, but patient eventually dies of the disease.
Tumor cell burden (log scale)
10^{12}
10^{10}
10^8
10^6
10^4
10^2
1 Kg mass
Death
Death
1 g mass
Cancer cells become increasingly less responsive to treatment
Patient symptomatic
Patient asymptomatic
Surgery
Treatment with anticancer drug
1mg mass
"Cure"
Time
CURATIVE CHEMOTHERAPY
(disseminated cancers, such as leukemia)
Combination drug therapy reduces chance of drug resistance.
Each drug is chosen to have a different cellular site of action or different cell cycle specificity.
Each drug is chosen to have a different organ toxicity.
CURATIVE CHEMOTHERAPY
(solid tumors, such as testicular carcinoma)
Tumor burden is initially reduced by surgery and/or radiation.
Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared.

Types of Cancer Treatment

- When cancer is diagnosed, the **tumor mass usually contains about 10^9 cells** in solid tumors.
- There are two main **types of treatment approaches**:

1. **Curative treatment:**
   - **Surgery** is used to **drastically reduce the tumor burden**.
   - **Chemotherapy** is then applied to **eliminate microscopic metastases** that were **not visible during surgery**.
   - This approach is used in **Wilms tumor (pediatric kidney cancer)**, **skin cancer**, **testicular cancer**, **acute lymphocytic leukemia**, and occasionally **melanoma**.
2. **Palliative chemotherapy:**
   - Aims to **relieve symptoms**, **reduce tumor size**, and **improve quality of life**.
   - It may **delay disease progression** but **is not curative**.

Treatment Outcomes in Acute Lymphoblastic Leukemia (ALL)

- **Adults**
  - Complete remission (CR): 80–85%
  - Leukemia-free survival (LFS): 30–40
- **Children**
  - Complete remission (CR): 95–99%
  - Leukemia-free survival (LFS): 70–80%

- **CR vs. LFS:**
  - **Complete Remission (CR):** Reduction of **blast cells in the bone marrow to below 5%**, with **no clinical symptoms** of leukemia, achieved in a **short period** after treatment.
  - **Leukemia-Free Survival (LFS):** A **sustained period without detectable leukemia cells**, indicating **long-term remission**.

Cancer in Adults: Mutation Accumulation and Immune Evasion

- **Cancer in adults** tends to have **more accumulated mutations** and **longer development time**, allowing the malignant cells to become **highly adapted to their environment**. Although the **adult immune system is more mature**, cancer cells often **evolve mechanisms to evade immune detection**, making treatment more challenging.

Combination Chemotherapy

- We use combination chemotherapy in order to :-
  1. Obtain synergistic action
  2. Minimize side effects.
  3. Attack leukemic cells in different phases of mitosis.
  4. Delay the onset of resistance of the malignant cells.

Effective Drugs for ALL

1. Vincristine → Arrest cell mitosis
2. Prednisone → Lympholysis
3. 6-M.P. → Inhibit DNA synthesis
4. Methotrexate → Inhibit RNA and protein synthesis
5. Doxorubicin (Adriamycin) → Inhibit DNA synthesis
6. L-asparaginase

- We use this treatment for 3 years in males and 2 years in females because cancer is more aggressive in males.

Chemotherapy for Acute Leukemias

- Phases of ALL treatment:
  1. Induction of remission (4 to 6 months)
     - During the **induction phase, chemotherapy suppresses bone marrow activity**, eliminating both **normal and malignant cells**. This **bone marrow suppression** can lead to **neutropenia**, and if accompanied by fever, it is known as **febrile neutropenia**, a potentially **life-threatening complication** that requires immediate medical attention.
     - Aims to **eliminate most leukemic cells** and achieve **complete remission** (<5% blasts in bone marrow).

Post-remission Therapy

  2. Intensification
     - Uses **high-dose chemotherapy** to destroy **remaining leukemic cells** and prevent early relapse. **Doses are often lower** than in initial induction.
  3. CNS prophylaxis
     - Prevents **leukemic infiltration of the central nervous system** using **intrathecal chemotherapy** (e.g., methotrexate).
  4. Maintenance
     - Long-term, low-dose chemotherapy to **sustain remission** and **prevent relapse** over several years.

Induction

- **Four to six weeks**:
  - Vincristine: Acts on mitosis, arresting cells in the M phase.
  - Glucocorticoid (prednisone, prednisolone or dexamethasone): Directed toward lymphatic cells.
  - L-asparaginase
- **Important:** Never combine **two drugs with the same mechanism of action**, as the goal of combination therapy is to achieve a **synergistic effect** by targeting **different pathways** in cancer cell growth.

PHARMACOLOGY QUIZ

LECTURE 4

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			