Tumour 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 tumour suppressor genes which function in various biochemical processes.

Tumour Biology

(3) Damage is also done to DNA repair genes so that, over time, giving rise to hypermutability and tumour heterogeneity.

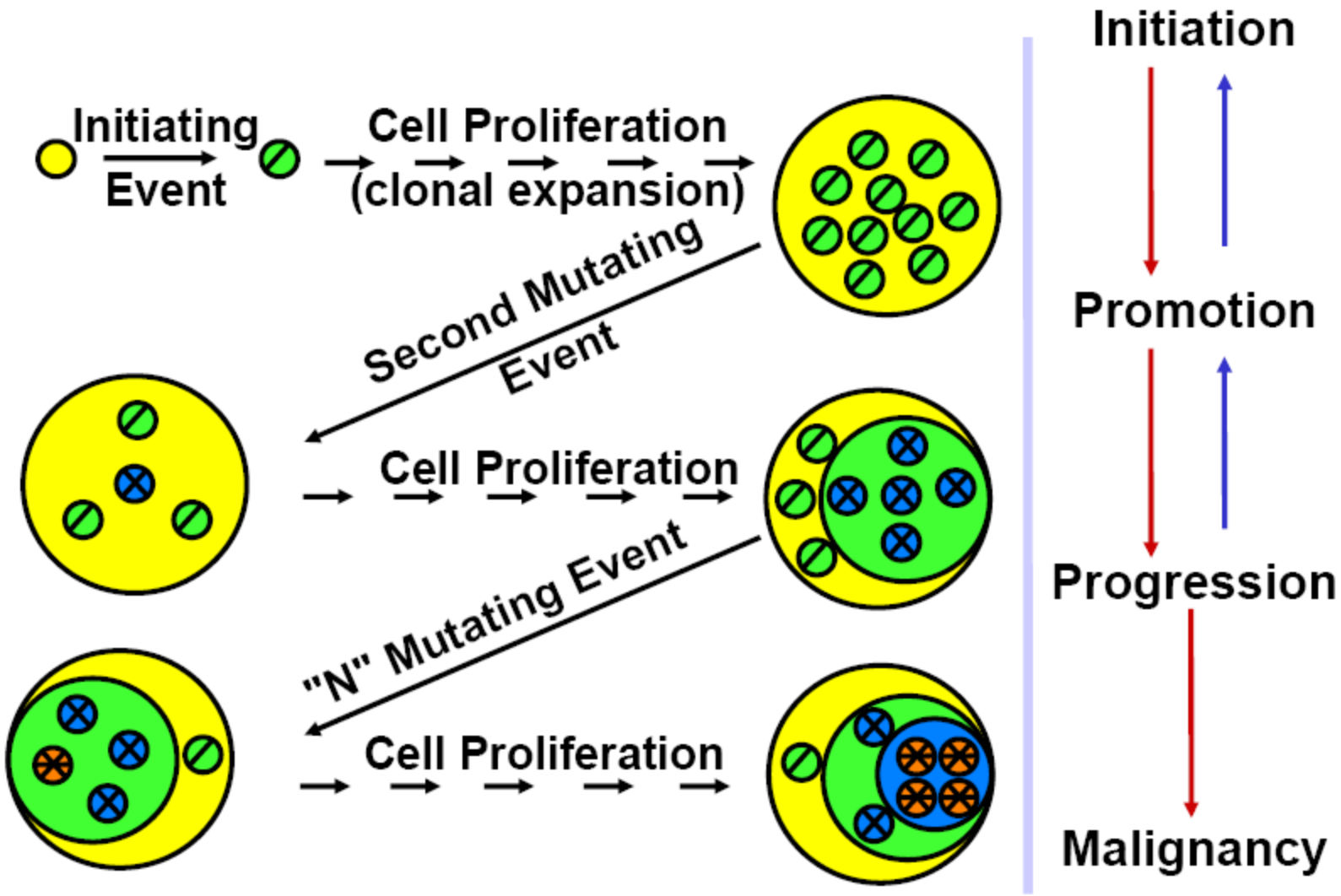
The outcome is that tumour cells relentlessly drive through the proliferative cell cycle and generally loose the capacity to differentiate.

(4) To become MALIGNANT

a. The mutated cells have to acquire the capacity to avoid immune detection to metastasise and

b. to be able to induce angiogenesis in order to provide themselves with a blood supply.

Stages of Carcinogenesis

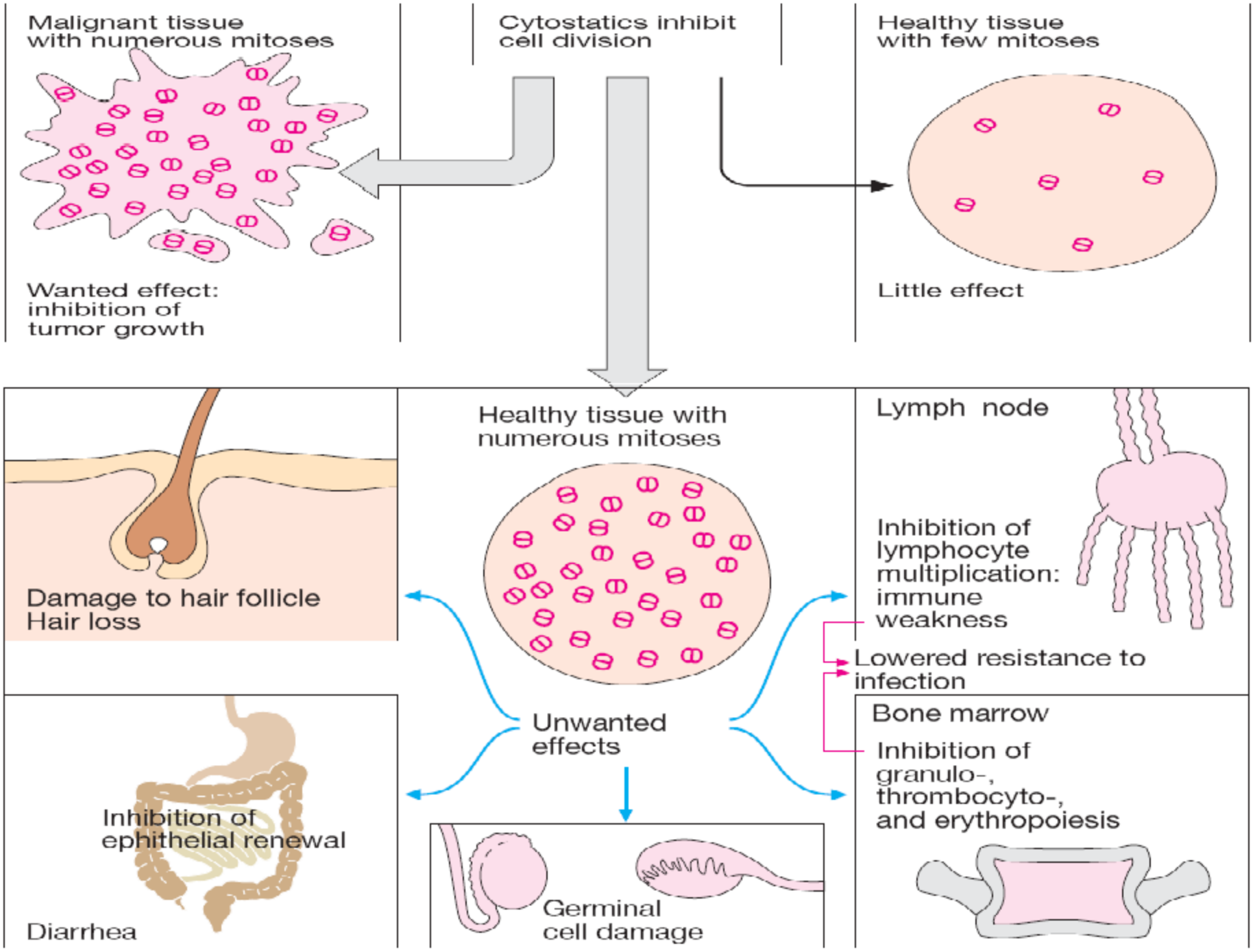


Cancer Chemotherapy

- **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.**

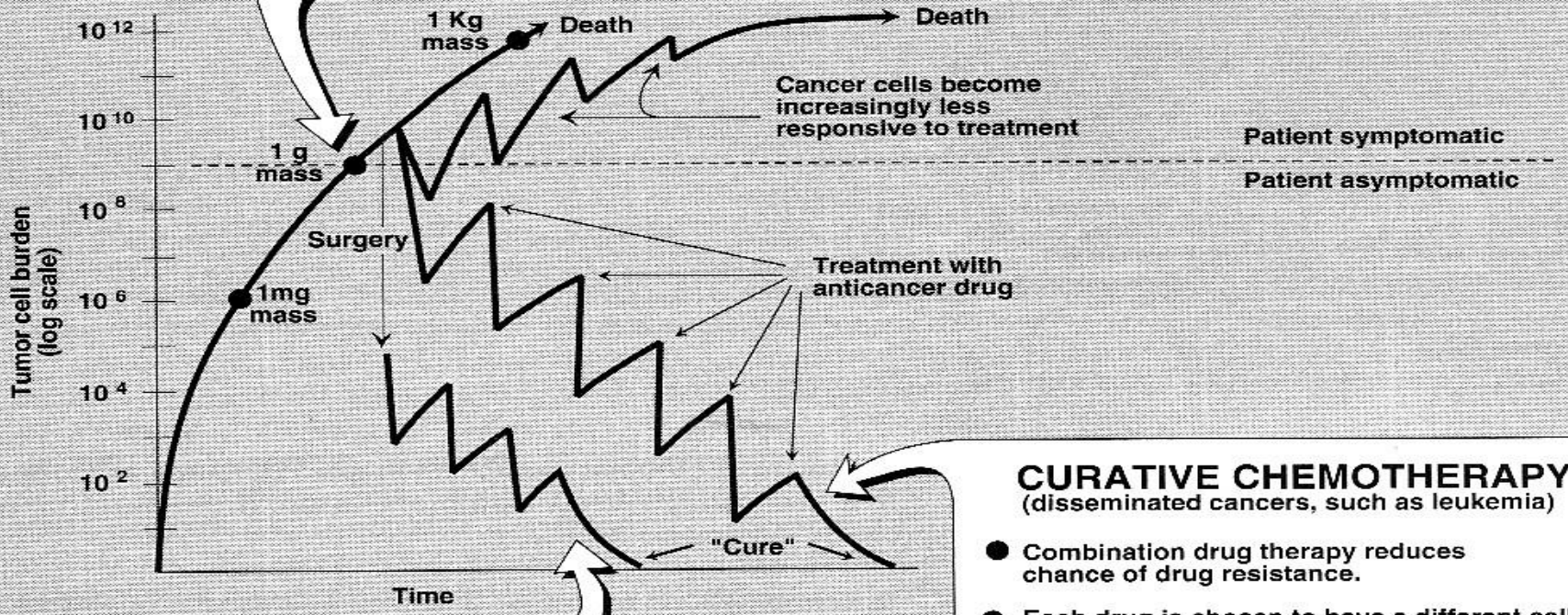

Malignant tissue with numerous mitoses
Cytostatics inhibit cell division
Healthy tissue with few mitoses
Wanted effect: inhibition of tumor growth
Little effect
Damage to hair follicle
Hair loss
Healthy tissue with numerous mitoses
Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered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

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.



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.

Treatment results in 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%**

Combination chemotherapy

- **in order to :-**

1. **obtain synergestic action**

2. **minimize side effects.**

3. **attacks 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- predinsone ----> Lyrmpholysis

3-6.M.P. ----> inhibit DNA synthesis.

4-Methotrexate ----> inhibit RNA and protein

Synthesis

5-Doxorubich (adriamycin)----> inhibit DNA synthesis

6-L- asparaginase

Chemotherapy for acute leukemias

- Phases of ALL treatment
  - induction
  - intensification
  - CNS prophylaxis
  - maintenance

} post-remission therapy

Induction

four to six weeks:

- Vincristine
- Glucocorticoid (prednisone, prednisolone or dexamethasone)
- L-asparaginase

Pharmacodynamics

- The malignant cells are dependent on an exogenous source of asparagine for survival.
- Normal cells, however, are able to synthesize asparagine and thus are affected less by the rapid depletion produced by treatment with the enzyme asparaginase.

L-Asparaginase – Mechanism of Action

- Catalyzes the conversion of L-asparagine to aspartic acid and ammonia.
- Reversal of L-asparagine synthetase activity.
- Results in rapid and complete depletion of L-asparagine.
- Lack of intracellular asparagine results in decrease of protein synthesis and apoptosis.

L-Asparaginase – Impaired Protein Synthesis

- Decreased production of insulin
  - Resultant hyperglycemia secondary to hypoinsulinemia
  - Hyperglycemia usually transient and resolves upon discontinuation
    - Blood sugar should be closely monitored

- Decreased production of albumin
  - Hypoalbuminemia can be severe resulting in peripheral edema or ascites
    - Patients with limited hepatic synthetic function may be unable to tolerate the effects of L-asparaginase

L-Asparaginase – Impaired Protein Synthesis

- Decreased production of vitamin K-dependent clotting factors and endogenous anticoagulants such as proteins C and S and antithrombin III
  - Coagulopathies, thrombosis, or bleeding due to impaired protein synthesis may occur
  - Monitor coagulation parameters during L-asparaginase therapy
  - Use cautiously in patients with a preexisting coagulopathy (e.g. hemophilia) or hepatic disease
  - Intramuscular injections may cause bleeding, bruising, or hematomas due to coagulopathy

L-Asparaginase – Toxicities

- Mild nausea/vomiting
  - Anorexia, abdominal cramps, general malaise, weight loss
- Tumor Lysis Syndrome (TLS)
  - Hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and decreased urine output
  - severe renal insufficiency

Vincristine

- Constipation is common during articularly because of the Vincristine.

- Nerve Irritation

Vincristine may cause numbness or tingling in the hands and feet. If this occurs.

GLUCOCORTICOIDS

- **have inhibitory effects on lymphocyte proliferation and are used in treating lymphomas and leukaemias.**

- **REDNISONE is an example; that used to induce remission in the treatment of lymphocytic leukaemia and in the treatment of Hodgkin and non Hodgkin lymphoma.**

Steroid Side Effects

- : Potential side effects of the steroid prednisone can include: trouble sleeping, increased appetite, fluid retention and swelling, indigestion, restlessness, nervousness, headache, blurred vision, muscle cramps and weakness, increased blood sugar level, bone pain, and high blood pressure.

Consolidation

- Once normal haematopoiesis is achieved, patients undergo **Consolidation** therapy.

- Common regimens in childhood ALL include:

1. **Methotrexate with mercaptopurine**

2. High-dose asparaginase over an extended period

3. Reinduction treatment (a repetition of the initial induction therapy in the first few months of remission).

Maintenance

- Maintenance usually consists

1. weekly methotrexate and
2. daily mercaptopurine.

- 2-3 years

CNS prophylaxis

- Patients with ALL frequently have meningeal leukaemia at the time of relapse (50-75% at one year in the absence of CNS prophylaxis) and a few have meningeal disease at diagnosis (<10%).

- Intrathecal (methotrexate, cytarabine, steroids)

- **and for adult high-dose systemic chemotherapy (methotrexate, cytarabine, L-asparaginase)**