Chemotherapy

TREATMENT MODALITIES

- Surgery
- Radiotherapy
- Systemic therapies:
  - Chemotherapy
  - Hormonal therapy
  - Immunotherapy
  - Biological (targeted) therapies

Systemic Anti-cancer therapies (SACT)

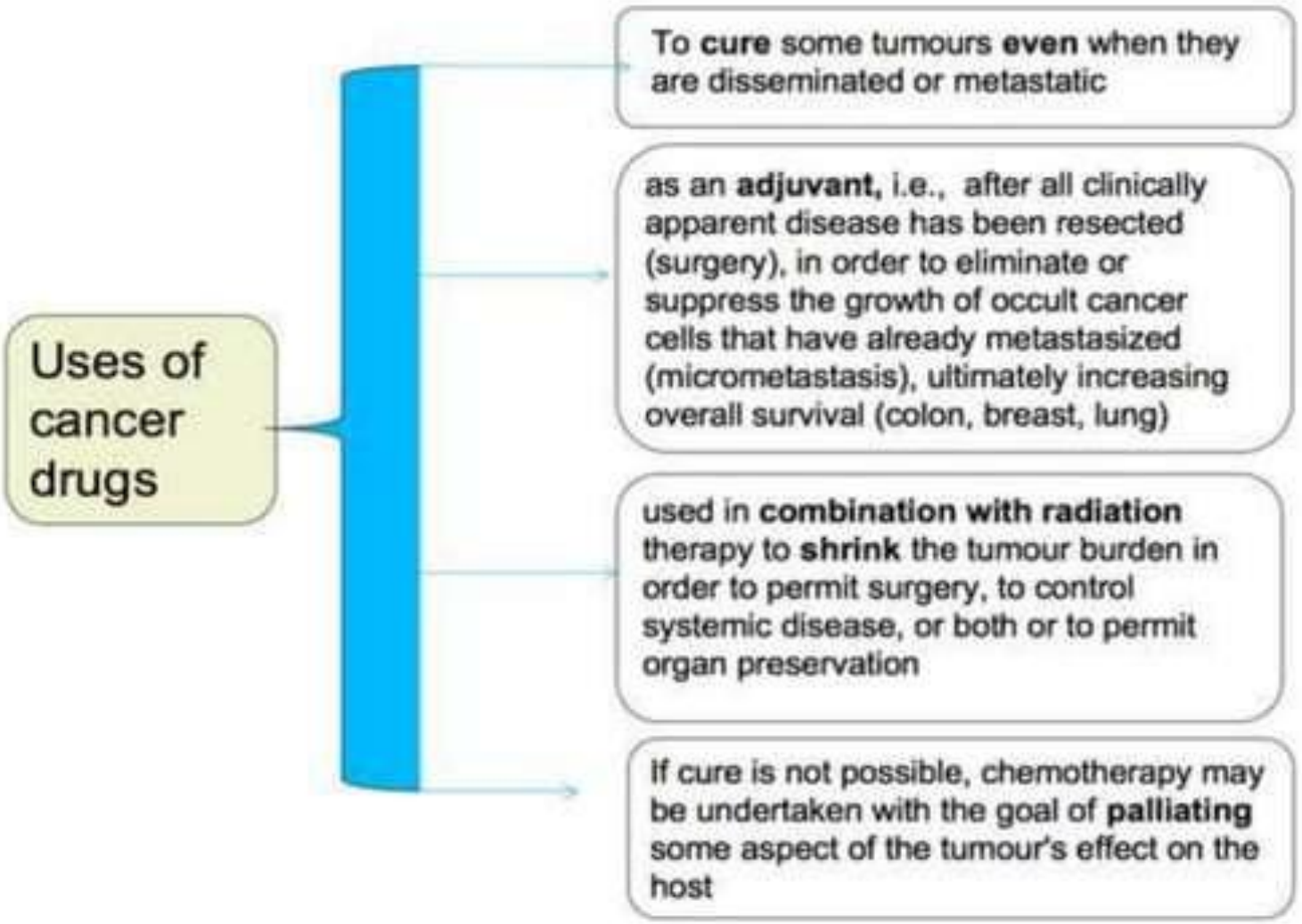
- Cancer is a "systemic" disease - roughly 50% patients will develop metastatic disease
- Systemic therapy (drug therapy - cytotoxic agents, hormones, biologics) distributes widely through the body - normal and malignant tissues
- Local therapy (surgery, radiation) is directed to a defined area of documented or presumed disease

Goals of SACT

Systemic therapy can be given for:

- Cure
- Increase survival
- Palliate symptoms through disease control
- Neoadjuvant / induction treatment - when local treatment is insufficient and disease is proven to be disseminated beyond the scope of local therapy
- Adjuvant / preventive treatment - when there is a high risk of recurrence with local treatment alone

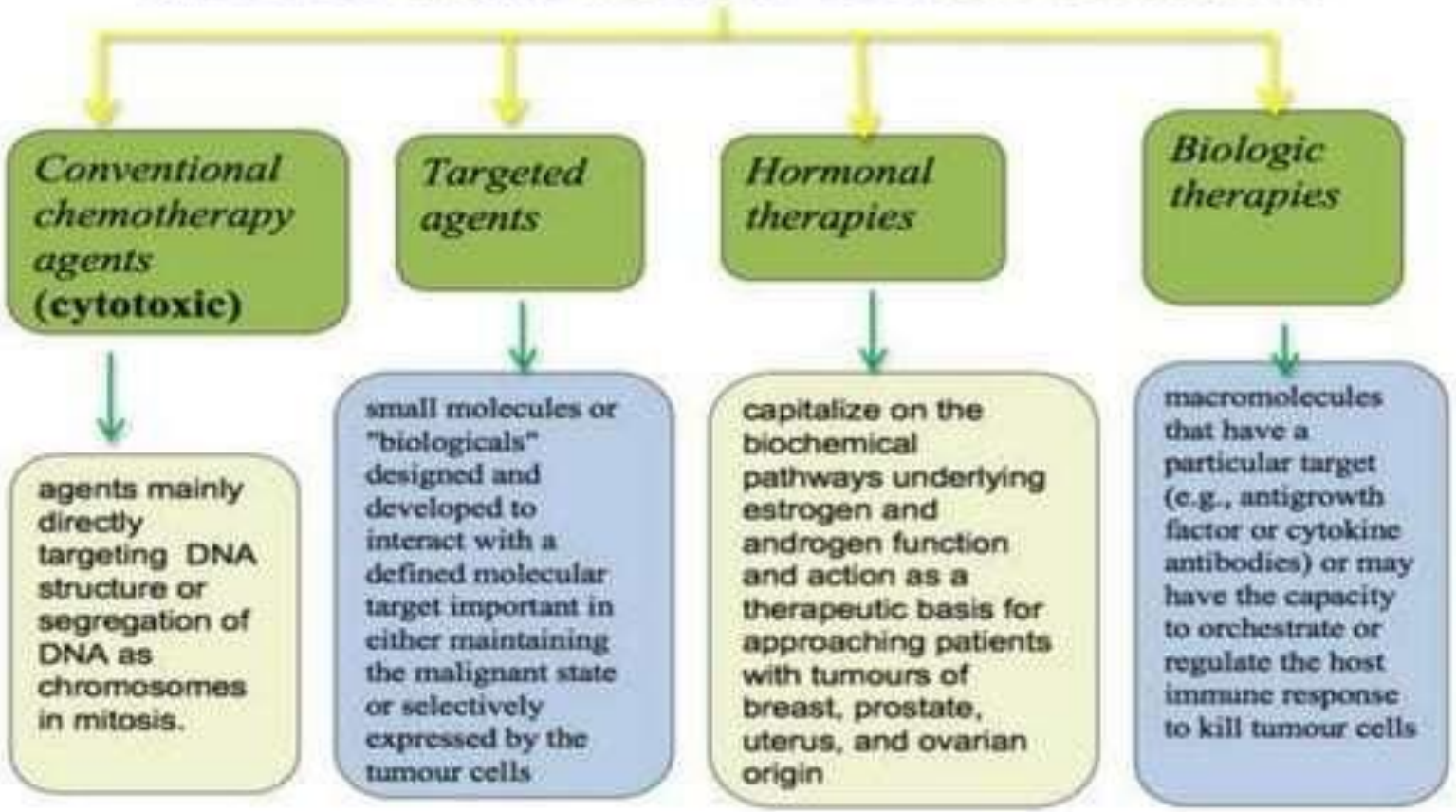
Goals of SACT



SACT

- Systemic therapy is based on the biology of cancer.
- Types of systemic therapy:
  - Cytotoxic agents (chemotherapy) eg Cisplatin, Etoposide
  - Targeted therapy , eg Gefitinib (tyrosine Kinase Inhibitors)
  - Endocrine/hormonal, eg Tamoxifen
  - Biologic therapies, eg Interferon

Types of drugs used in cancer treatment



Who gets SACT?

Factors to consider:

- Tumour factors
  - Stage
  - Pathological features
  - Treatment intent
- Patient factors
  - Fitness for treatment
  - Co-morbidity
  - Patient wishes

Fitness for treatment

Performance status:

- An attempt to quantify patients' wellbeing

Scoring systems:

- Karnofsky score
- WHO/ECOG score

WHO/ECOG score

0 - Asymptomatic

Fully active, able to carry on all activities without restriction

1 - Symptomatic

Ambulatory, able to carry out light work eg light housework

2 - Symptomatic

Up >50% of day, capable of all self care but unable to carry out any work activities

3 – Symptomatic

>50% of day in bed but not bedbound (limited self-care)

4 - Bedbound

Completely confined to bed/chair; incapable of self care

Chemotherapy

- The aim of chemotherapy is *"to do the maximum damage to cancer cells while causing the minimum damage to healthy tissue."*
- It is the use of cytotoxic drugs to destroy cancer cells
- Chemotherapy affects the entire body.
- This in combination with it affecting both healthy and cancer cells means it can be quite aggressive.
- However it is used widely today because of its ability to reduce and even eliminate cancer.

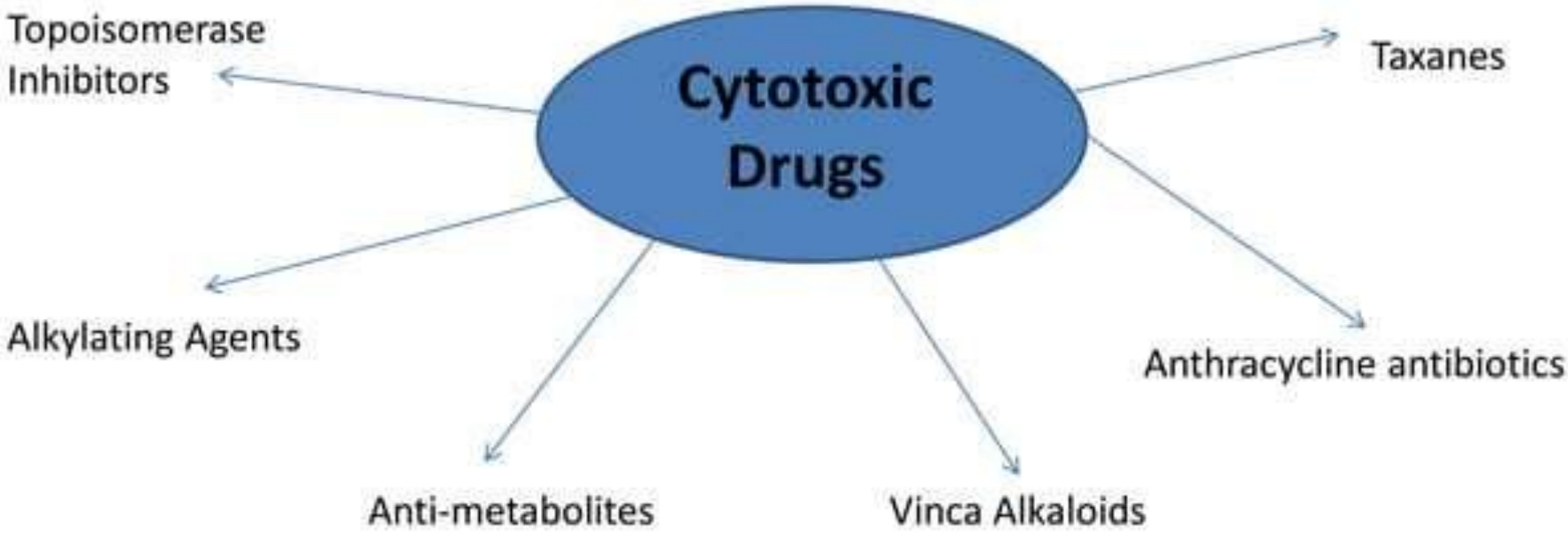
THE IDEAL TARGET FOR CANCER THERAPY

- Has a high level of expression in neoplastic tissues
- Plays a fundamental role in the pathogenesis of the cancer
- Does not have a vital role in normal tissues
- Target activation (eg phosphorylation) correlates well with its function
- Can be inhibited pharmacologically
- Target inhibition results in anti-tumor effects

THE IDEAL AGENT FOR CANCER THERAPY

- Has a high specificity and affinity for its target
- Interaction with target results in anti-tumor effects
- Has predictable and consistent pharmacological attributes
- Has minimal normal tissue toxicity
- Agent is easy to administer and ideally suitable for chronic administration e.g. oral use
- Potential application in either prevention or therapy of cancer

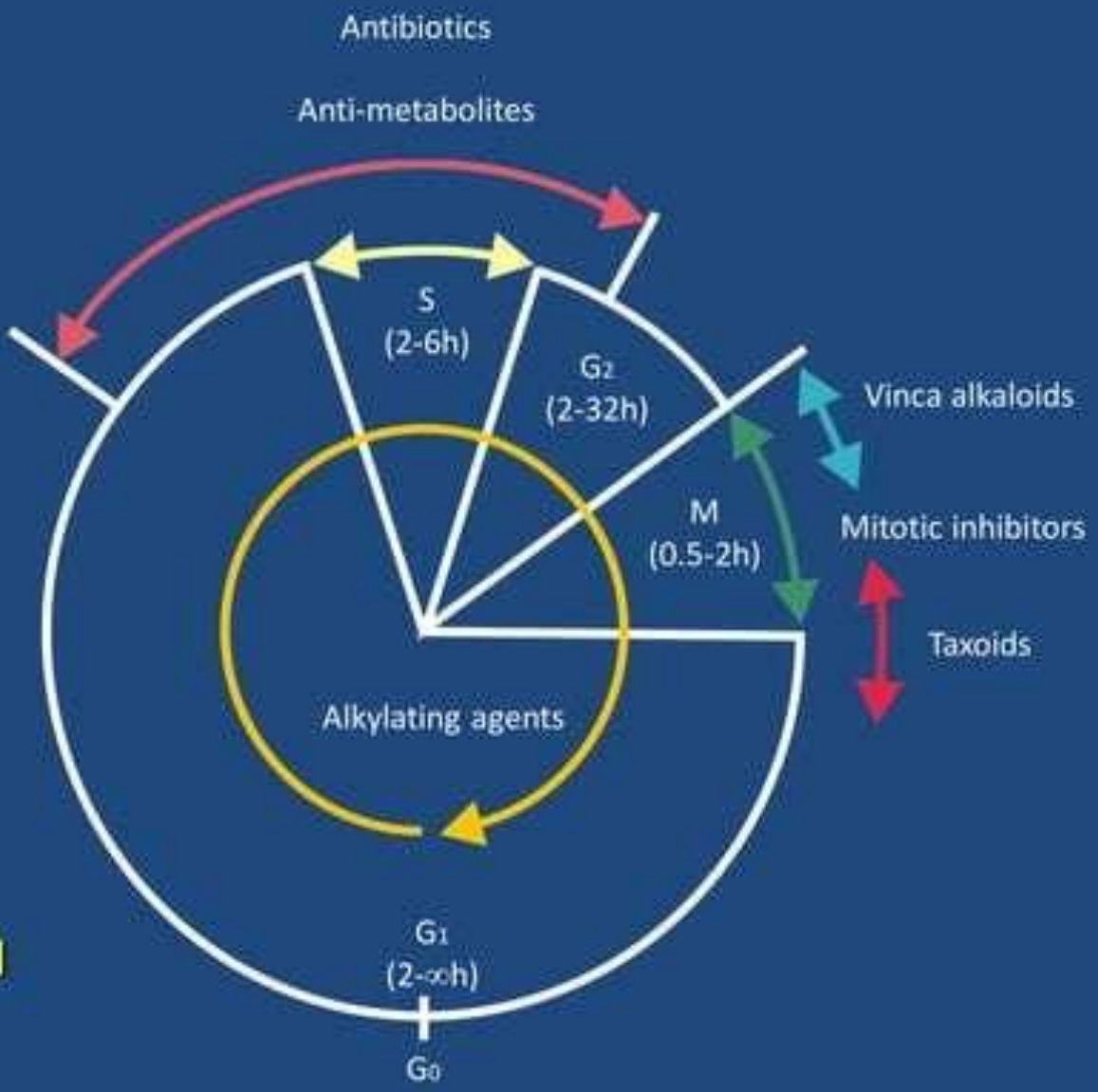
There are over 50 different cytotoxic drugs available



HOW DOES CHEMOTHERAPY WORK?

- Tumour cells have poor DNA repair mechanisms
- Normal cells can repair or replace themselves more efficiently
- Intermittent chemotherapy damages **both** normal replicating cells **and** tumour cells but the tumour cells do not recover as quickly
- DNA damage may prevent production of daughter cells or cause cell death eg through induction of apoptosis

Action sites of cytotoxic agents



Cell cycle level

TABLE 1: Cell-cycle–phase-specific drugs

S phase–dependent	M phase–dependent
Antimetabolites	Vinca alkaloids[a]
Capecitabine	Vinblastine
Cytarabine	Vincristine
Doxorubicin	Vinorelbine
Fludarabine	Podophyllotoxins
Floxuridine	Etoposide
Fluorouracil	Teniposide
Gemcitabine	Taxanes
Hydroxyurea	Docetaxel
Mercaptopurine	Paclitaxel
Methotrexate	**G_2 phase–dependent**
Prednisone	Bleomycin
Procarbazine	Irinotecan
Thioguanine	Mitoxantrone
	Topotecan
	G_1 phase–dependent
	Asparaginase
	Corticosteroids

[a] Have greatest effects in S phase and possibly late G_2; cell blockade or death, however, occurs in early mitosis.

Adapted, with permission, from Dorr RT, Von Hoff DD (eds): The Cancer Chemotherapy Handbook, 2nd ed, p 5. East Norwalk, Connecticut, Appleton & Lange, 1993.

CLASSIFICATION OF CYTOTOXIC AGENTS

ALKYLATING AGENTS	ANTI-METABOLITES	MITOTIC INHIBITORS	ANTIBIOTICS	OTHERS
BUSULFAN	CYTOSINE	ETOPOSIDE	BLEOMYCIN	L-ASPARAGINASE
CARMUSTINE	ARABINOSIDE	TAXOIDS	DACTINOMYCIN	HYDROXYUREA
CHLORAMBUCIL	FLOXURIDINE	VINBLASTINE	DAUNORUBICIN	PROCARBAZINE
CISPLATIN	FLUOROURACIL	VINCRISTINE	DOXORUBICIN	
CYCLOPHOSPHAMIDE	MERCAPTOPURINE	VINDESINE	MITOMYCIN-C	
IFOSFAMIDE	METHOTREXATE		MITOXANTRONE	
MELPHALAN			PLICAMYCIN	

ANTI-TUMOUR ANTIBIOTICS

- Actinomycin, Mitomycin C, Bleomycin.
- Fungal in origin
- Fragment DNA and form free radicals
- Work throughout cell cycle
- Used in testicular and haematological cancers and sarcomas

Doxyrubicin and epirubicin are anthracycline antibiotics that are both cardiotoxic

Bleomycin is a non-anthracycline antibiotic but unlike **Mitozantrone and Mitomycin C** it does not cause significant bone marrow suppression.

ALKYLATING AGENTS

- The first cytotoxic drugs, includes cyclophosphamide and ifosfamide which are still used today
- Cross link DNA by binding irreversibly to the N7 atoms of guanine bases
- Main action is during the synthesis phase of cell cycle
- Synthetic drugs using reactive Pt species work similarly:

  Cisplatin, Carboplatin and Oxaliplatin
- Cause both intra- and inter- DNA strand linkage of guanine

  bases and prevent DNA splitting
- Used in many solid and haematological tumours

Alkylating agents:

- **Cyclophosphamide**
- **Chlorambucil**
- **Melphalan**

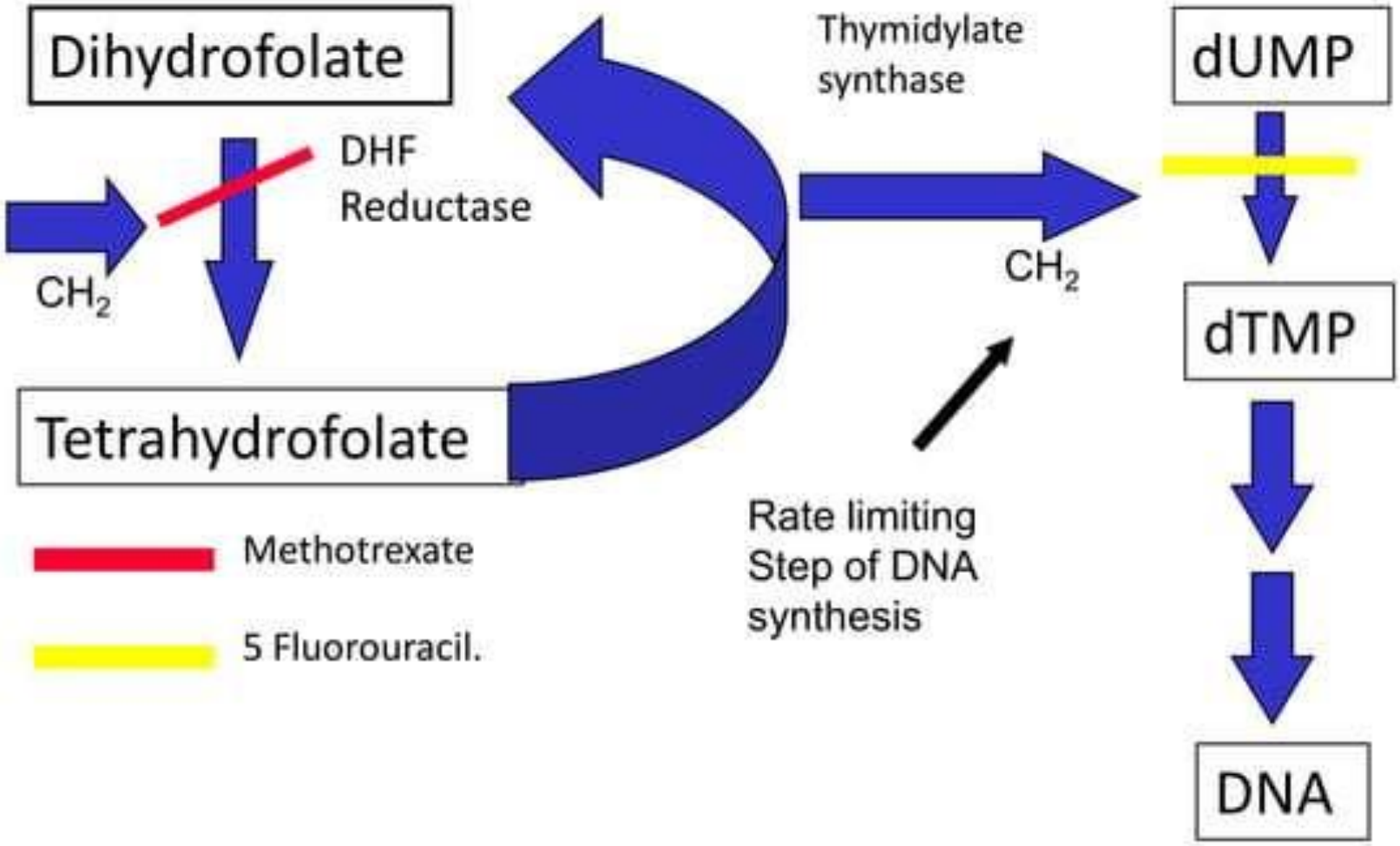
Non-classical alkylating agents

- **Cisplatin**
- **Carboplatin**

ANTI-METABOLITES

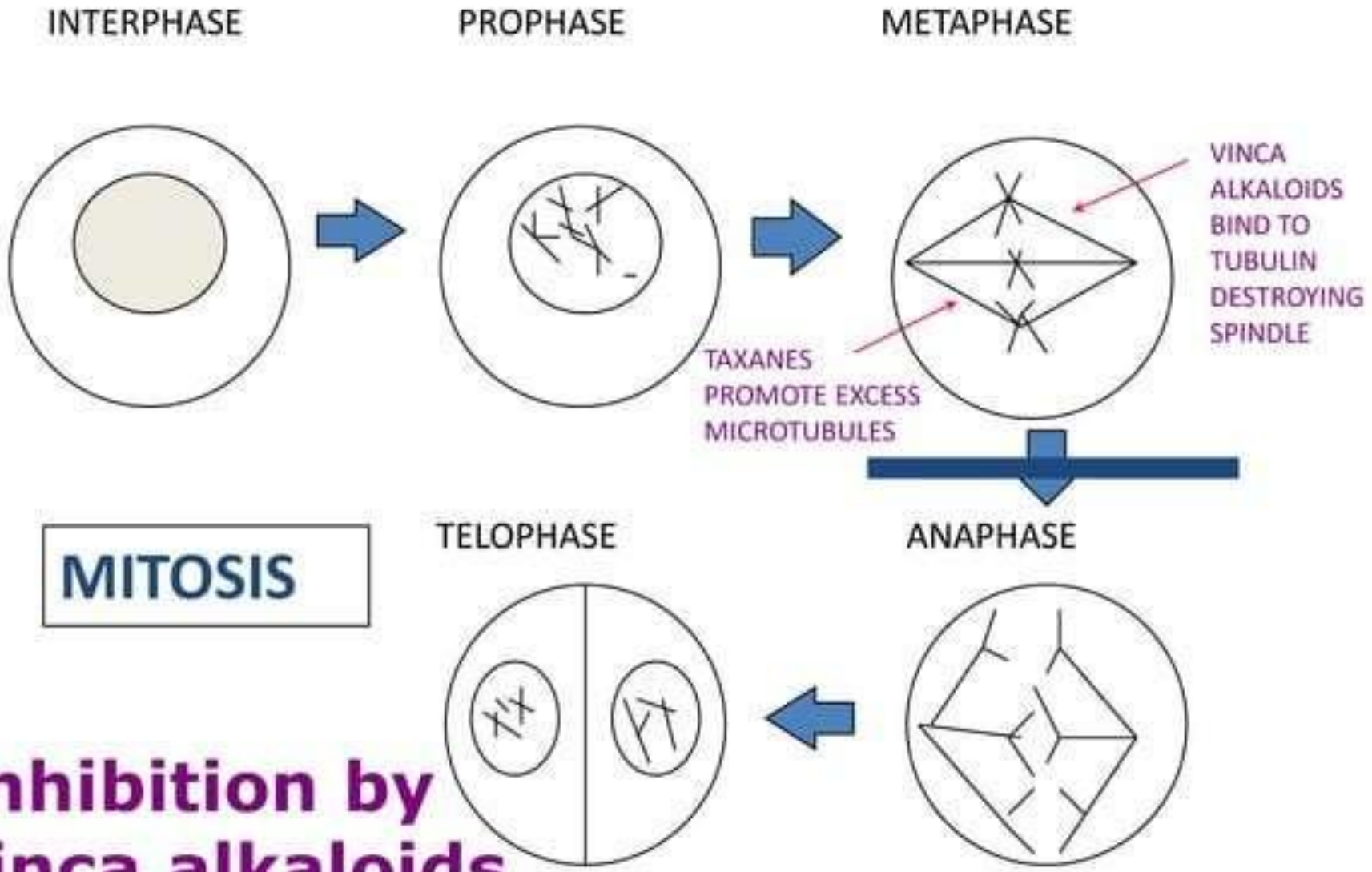
- Prevent synthesis of purines or pyrimidines which are required for formation of both DNA and RNA
- Similar in structure to natural metabolites
- Work in S phase of the cell cycle
- Examples : **Methotrexate, 5-Fluorouracil, Gemcitabine**
- Used in colorectal, breast and pancreatic cancers.

ANTI-METABOLITES



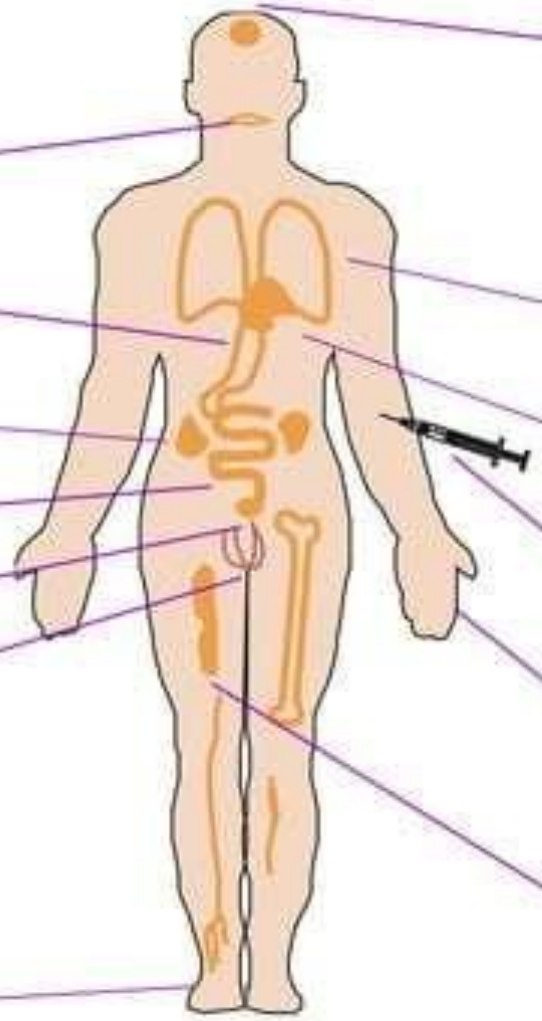
VINCA ALKALOIDS

- Derived from the periwinkle plant
- Bind to tubulin (building block of cell spindles)
- Cause metaphase arrest (in mitotic part of cell cycle)
- Examples : Vincristine, Vinblastine, Vinorelbine, Vinflunine
- Used in haematological, lung and breast cancers



Inhibition by vinca alkaloids and taxanes

Chemotherapy side effects



Hair loss

Mouth ulcers

Nausea/vomiting

Nephrotoxicity

Diarrhoea

Cystitis

Infertility

Neurotoxicity

Lung toxicity

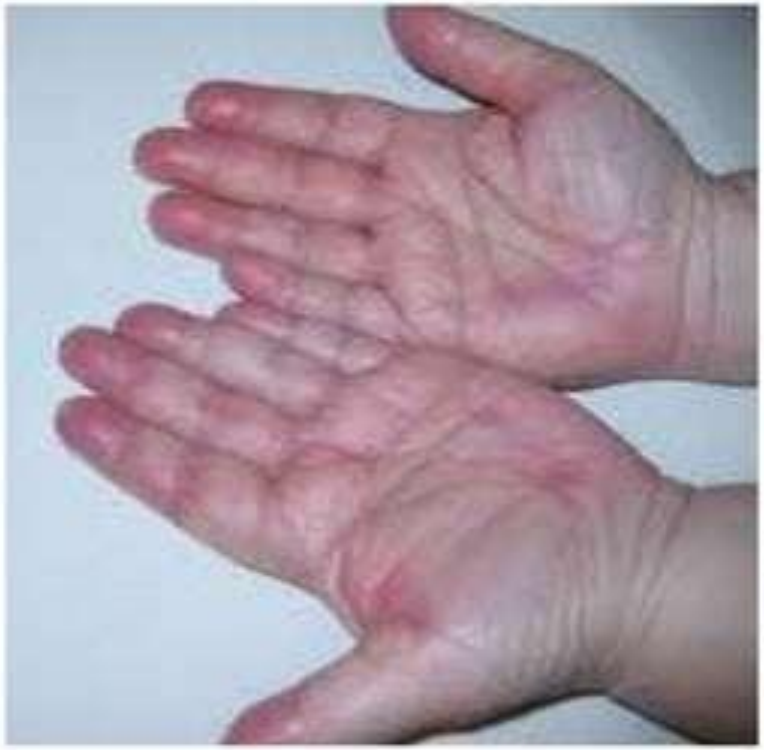
Cardiotoxicity

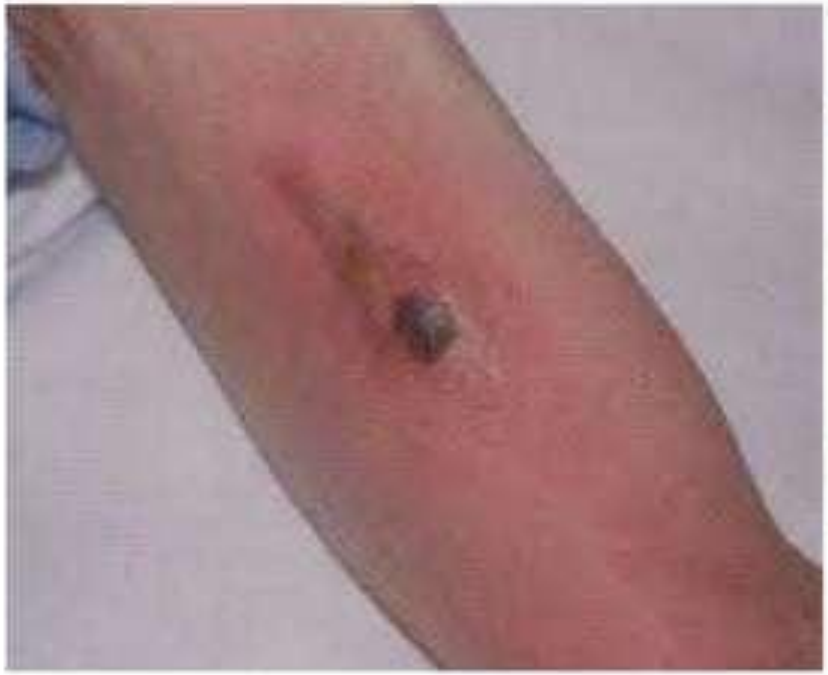
Local reaction

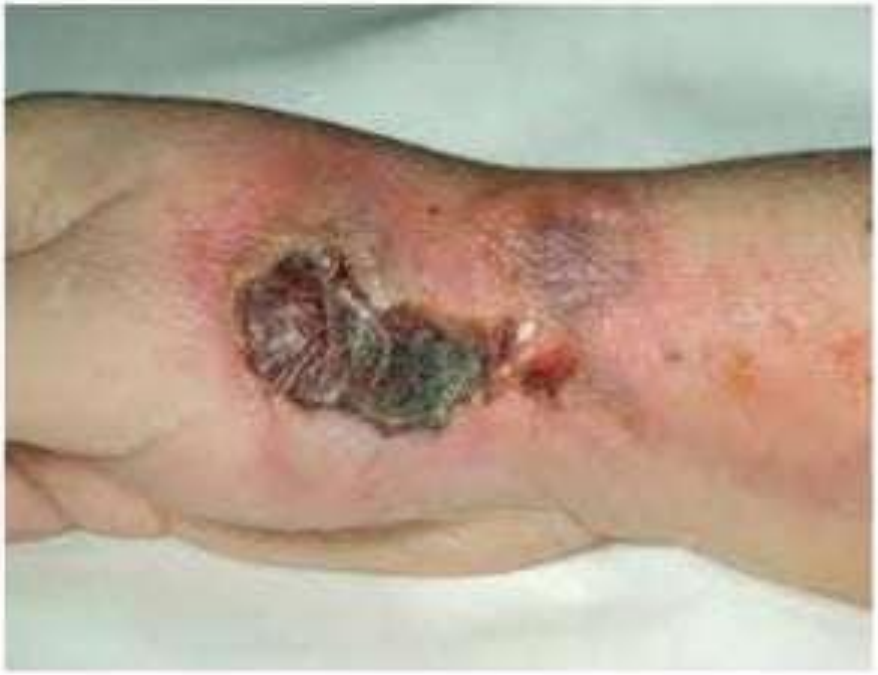
Skin changes

Bone marrow suppression

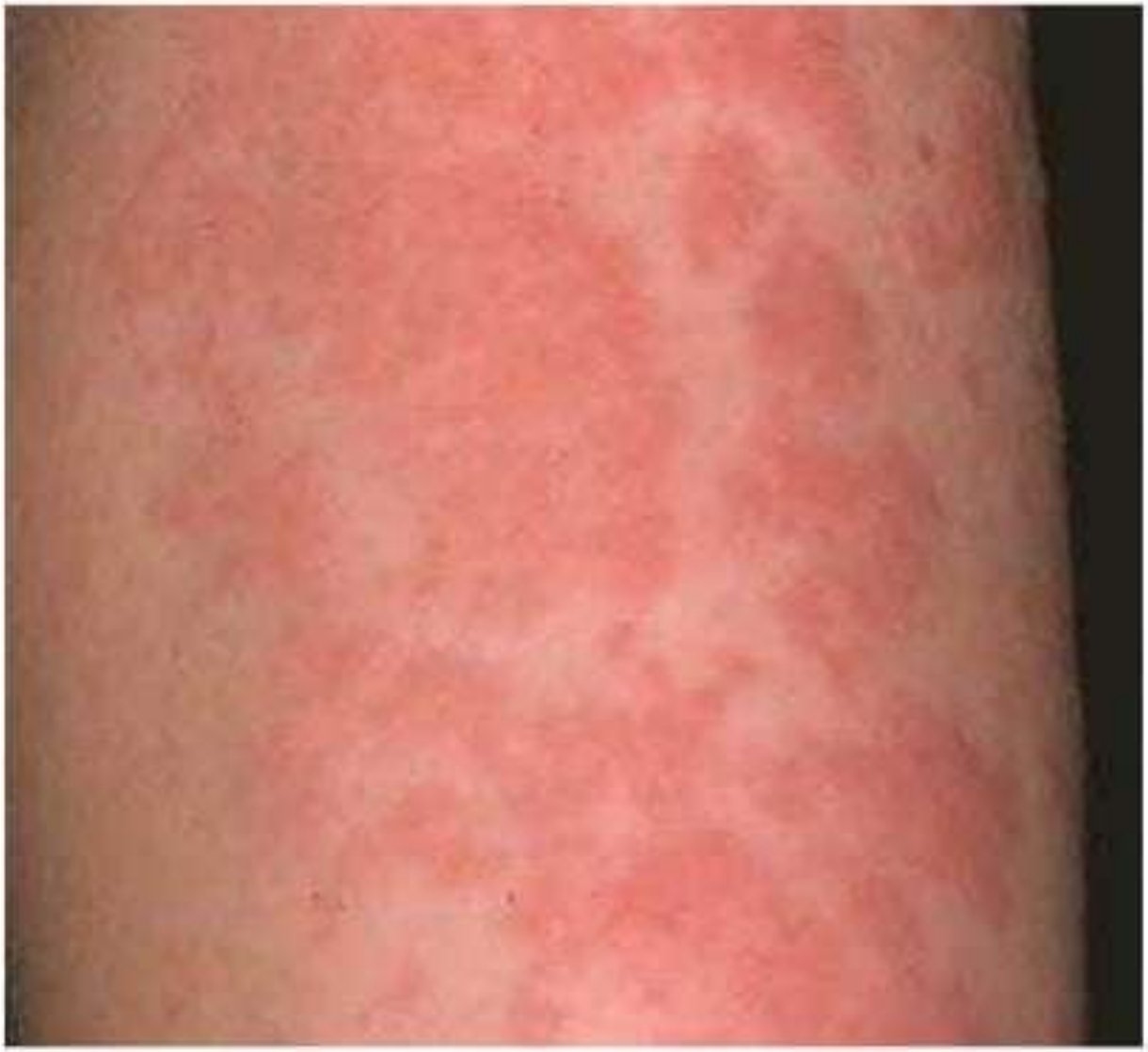
Hand-foot syndrome



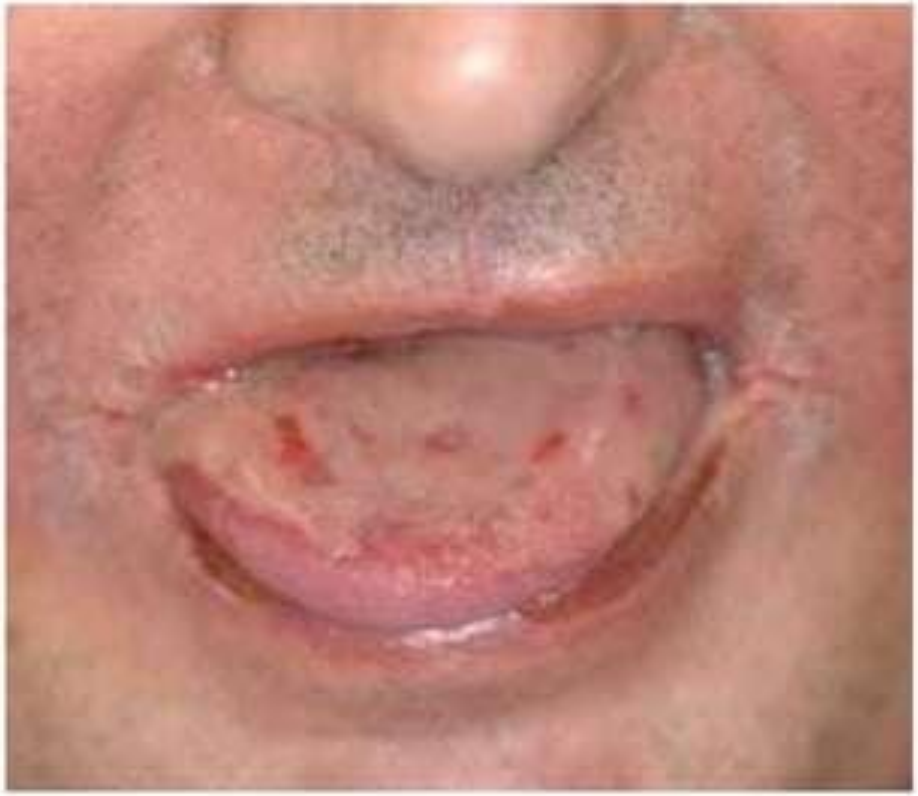


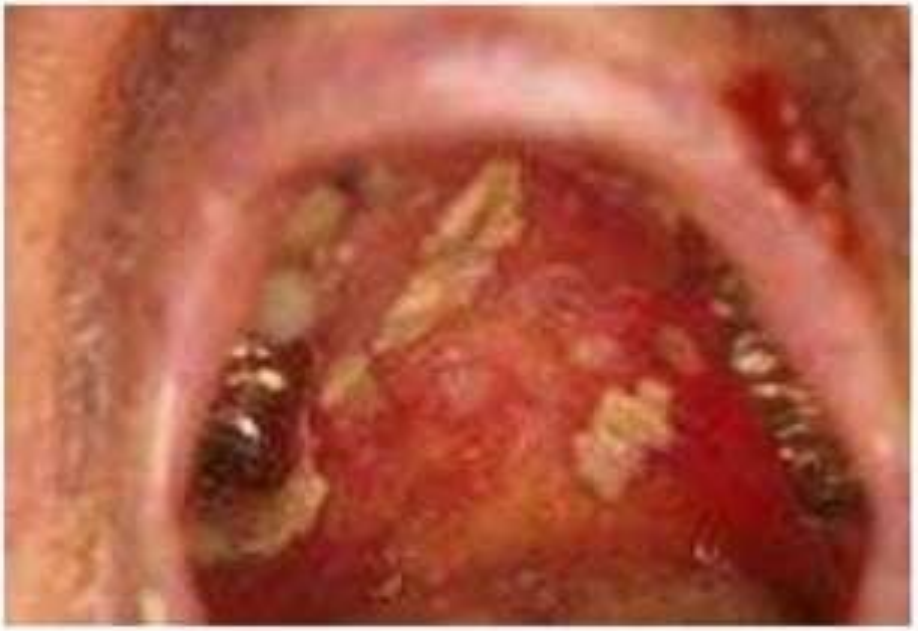


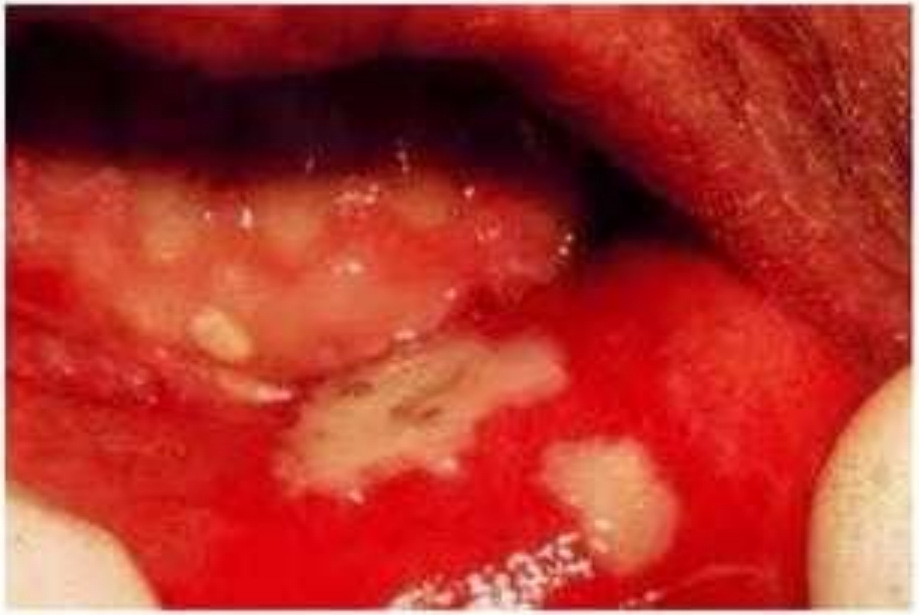
Chemotherapy extravasation



Allergic reaction







Mucositis

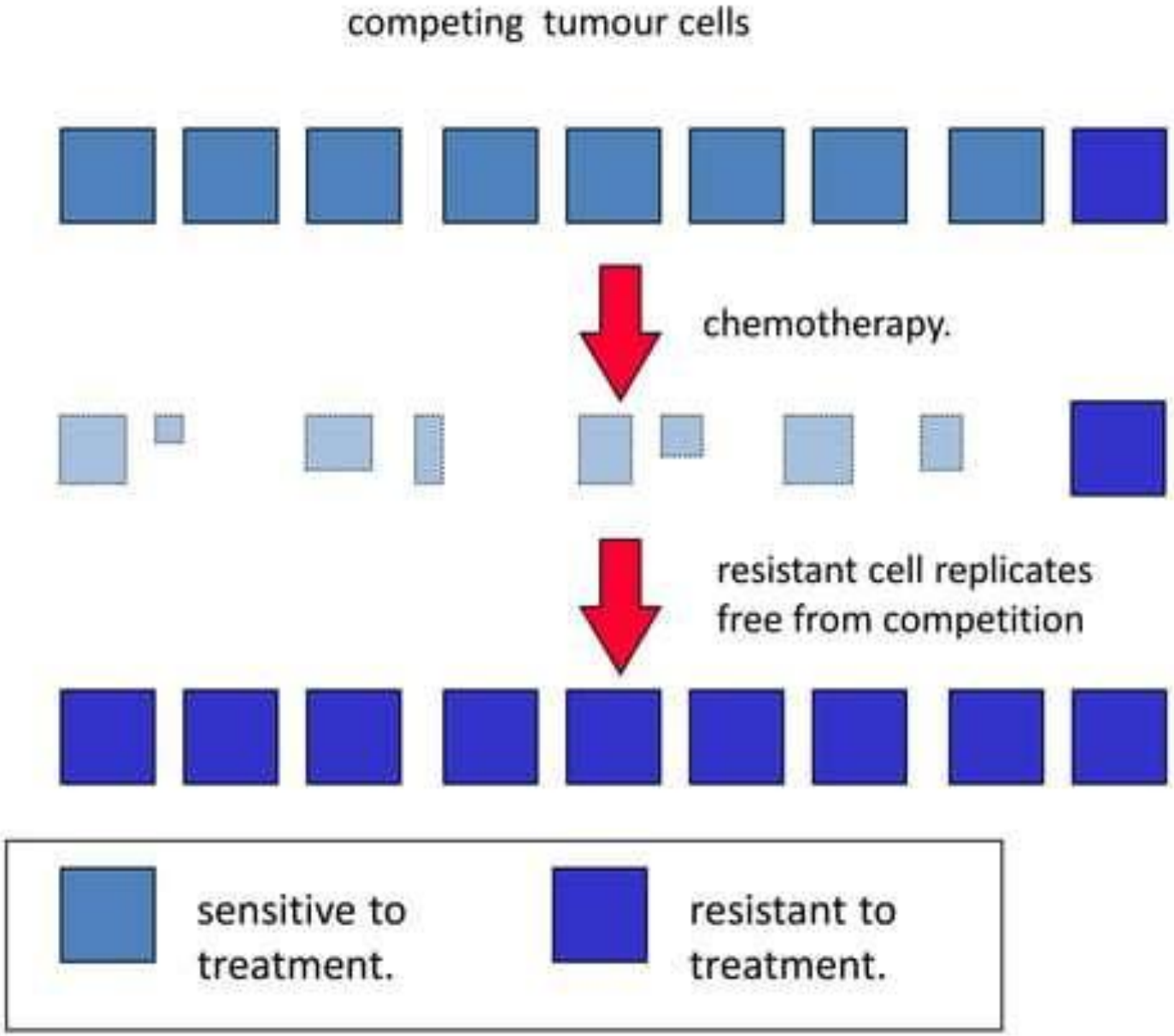
Toxicity Prevention

- Prophylactic anti-emetics
- Vascular access devices minimize extravasation
- Adequate pre/post hydration
- Stop below known toxic cumulative doses
- Dose reduction / delay
- Growth factor support
- Prophylactic antibiotics
- Mouth care
- Cytoprotectants / rescue agents

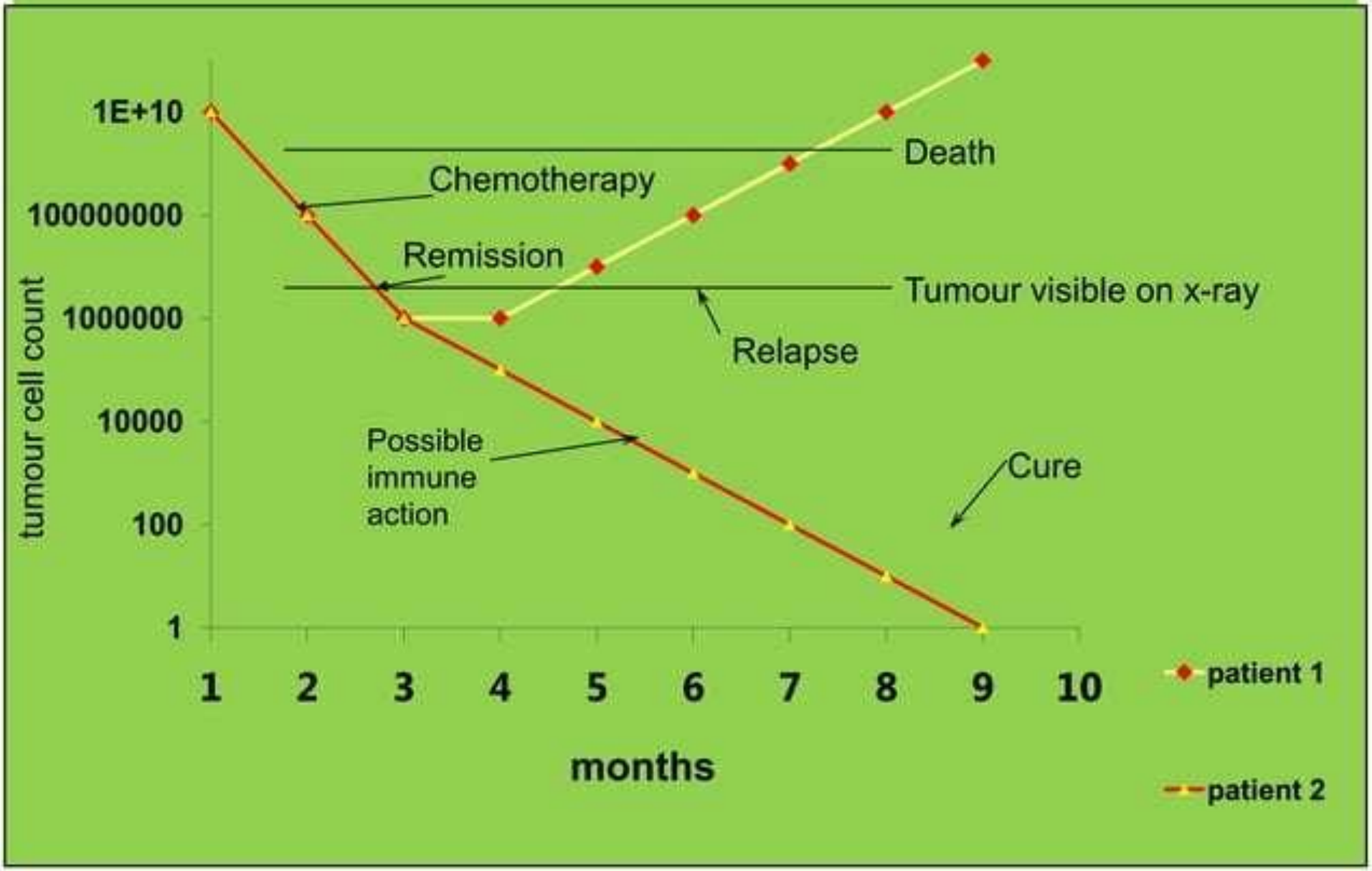
- Maintain a high index of suspicion and intervene early!

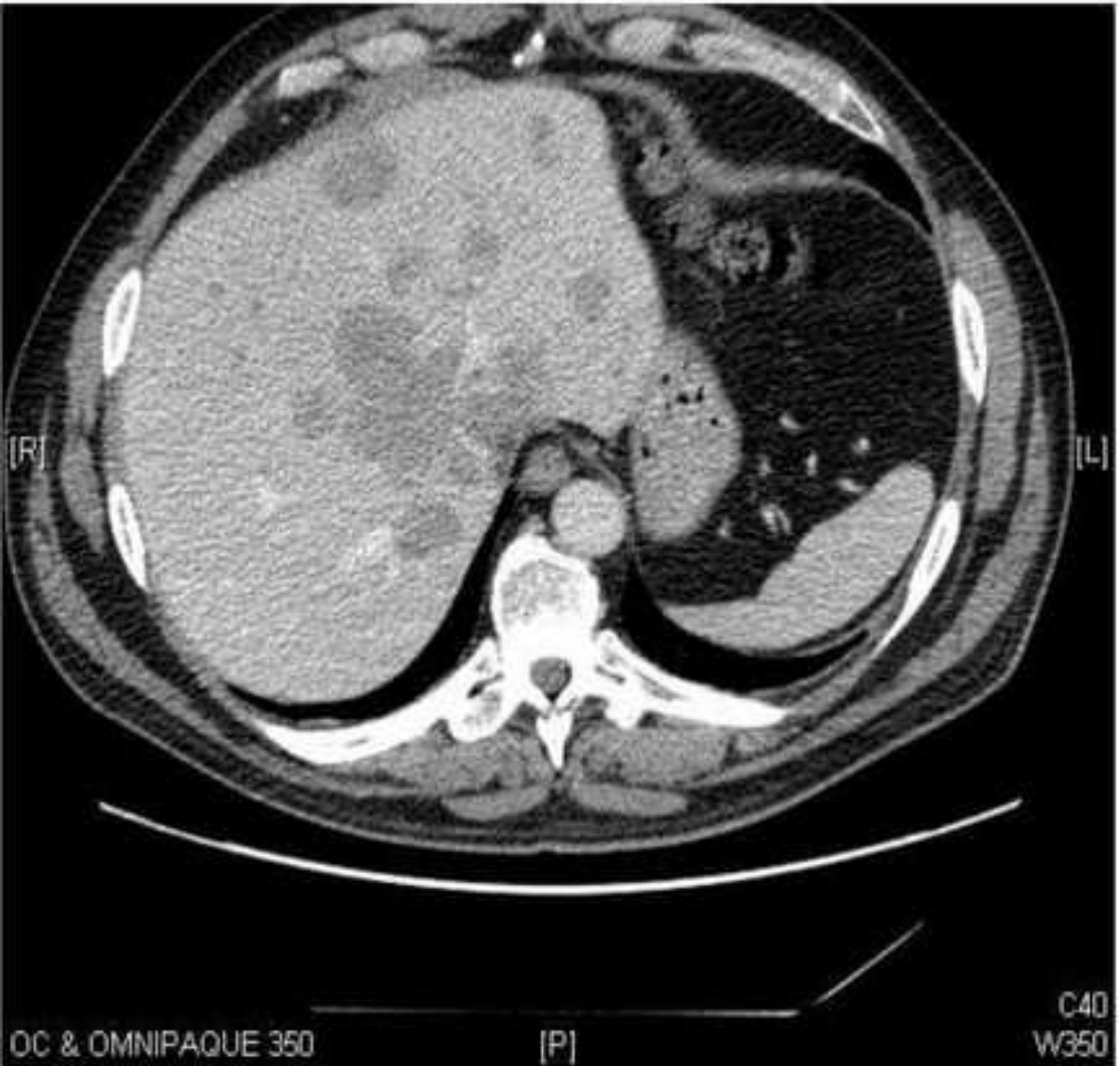
Why does chemotherapy fail?

- Primary resistance.
  - Tumour is not sensitive to selected treatment
- Secondary resistance.
  - Tumour becomes resistant to a treatment which originally caused a response
  - Natural selection (Darwinian theory)

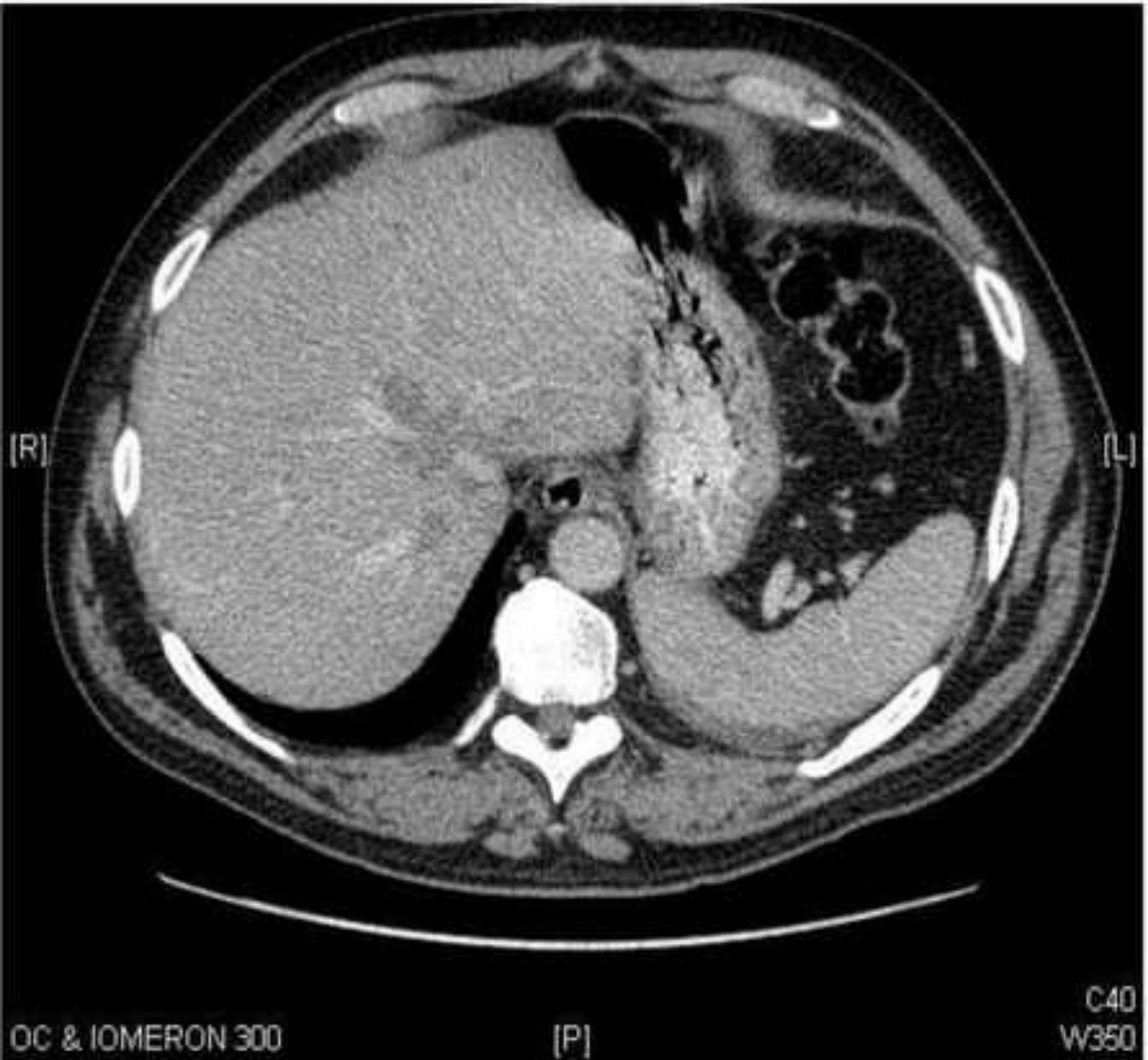

competing tumour cells
chemotherapy.
resistant cell replicates
free from competition
sensitive to
treatment.
resistant to
treatment.

RELAPSE VERSUS CURE

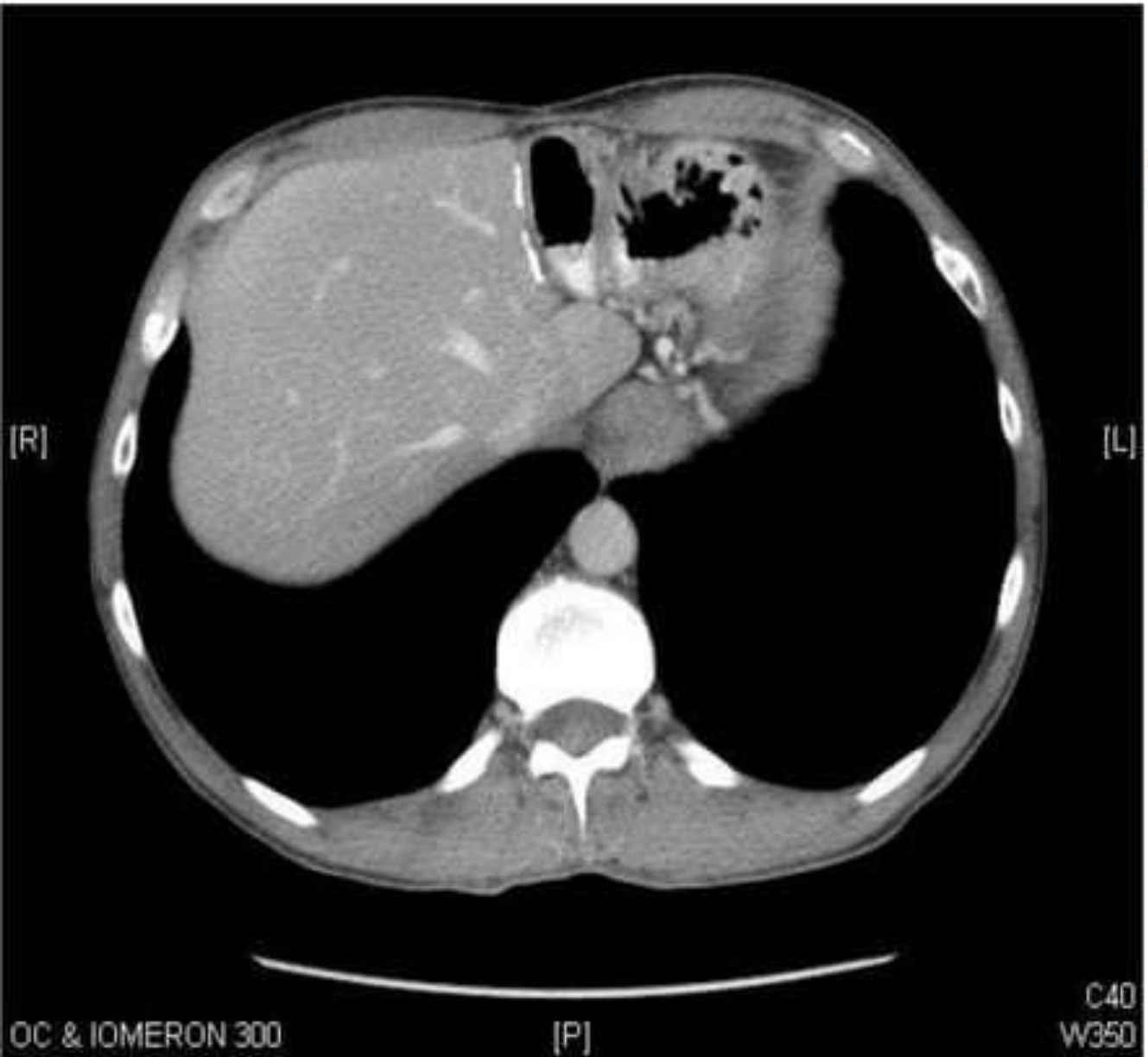




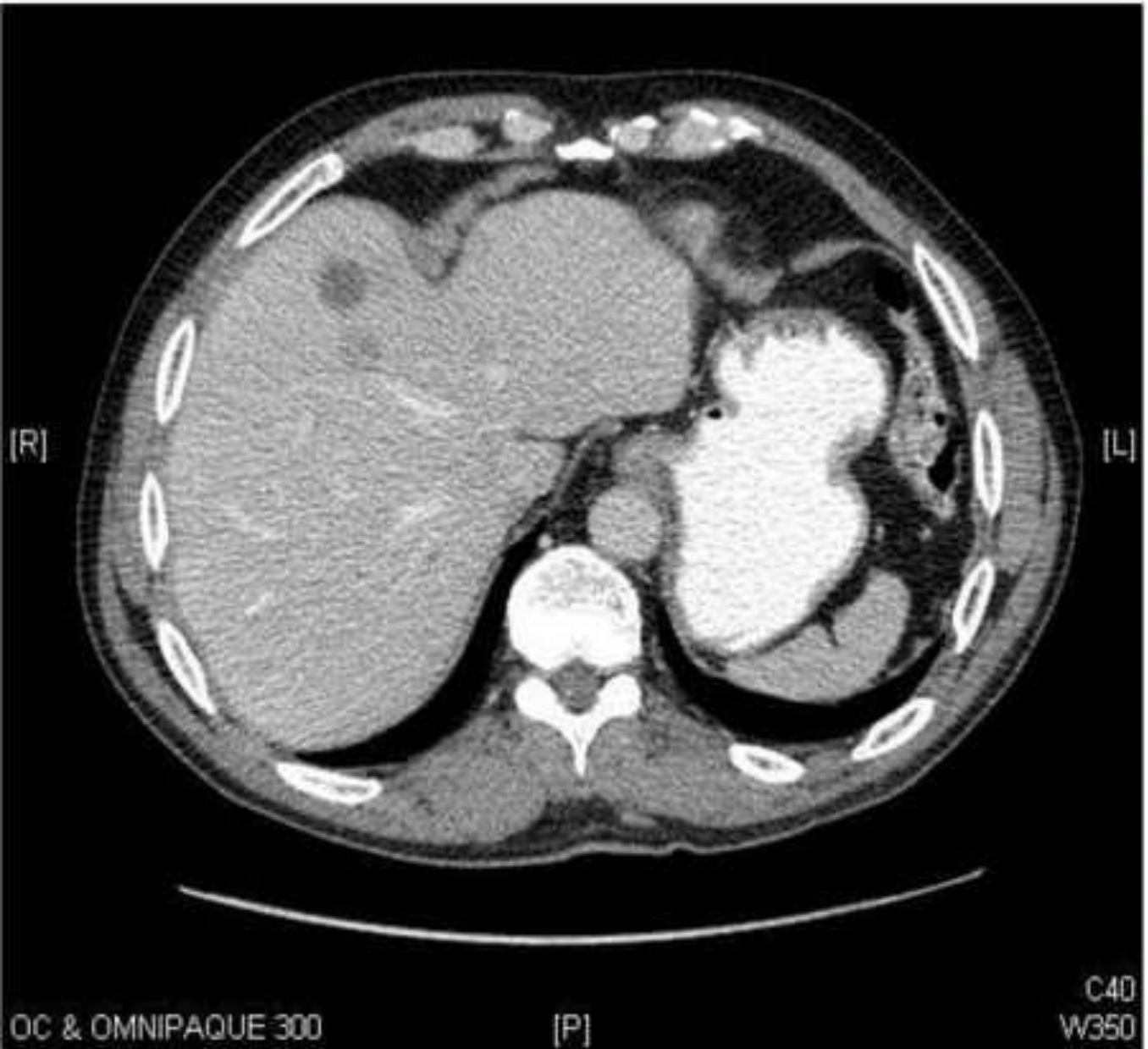
LIVER METS: BEFORE CHEMO



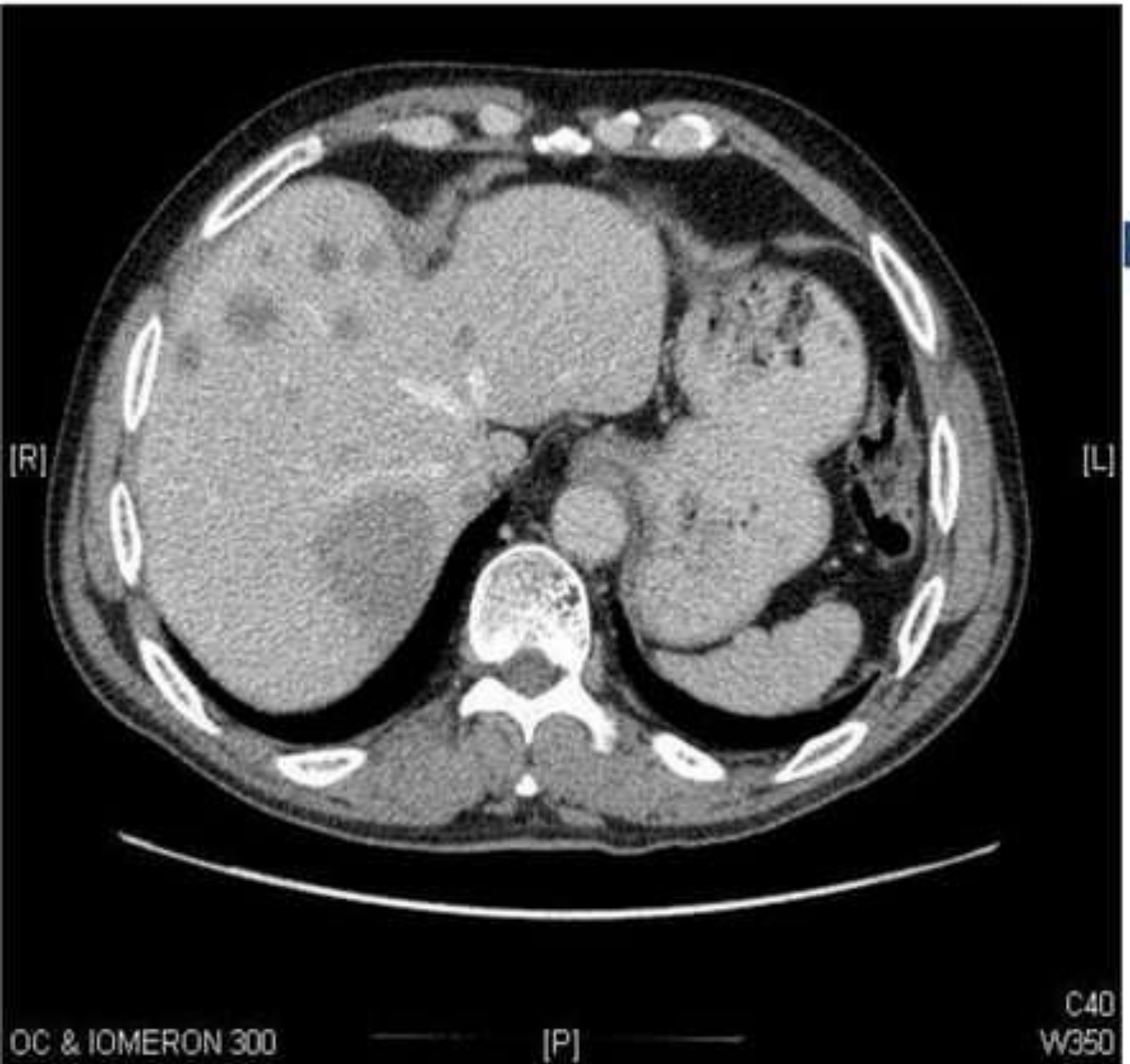
LIVER METS: PARTIAL RESPONSE ON CHEMO



LIVER AFTER RESECTION OF METASTASIS



LIVER METS: BEFORE CHEMO



LIVER METS: PROGRESSION ON CHEMO

Natural Selection Of Resistance

- Cancer cells originate from cellular mutations that prevent normal control of division
- Since tumour cells are unstable further mutations probable
- Some mutations may allow some of the tumour cells to resist cytotoxics. (around 10^8 cells dividing)

Mechanisms Of Resistance

- Alterations in cell membrane
- Increased drug deactivation
- Loss of drug activation
- Increased production of target molecule(s)
- Change in enzyme specificity
- Production of non-essential competitors, (decoys)
- Alternative Biochemical pathways
- Increased repair of damage to DNA

HOW TO AVOID RESISTANCE

- Treat when tumour is small (less likely to contain resistant cells)
- Use combinations of chemotherapy that are non-cross resistant and have different toxicity profiles:

  eg cisplatin and 5-fluorouracil
  - Alkylating agent to damage DNA
  - Anti-metabolite to prevent DNA synthesis and repair
- Use effective doses of chemotherapy drugs eg optimal supportive care to allow maintenance of dose intensity

IMMUNOTHERAPY: INTERFERONS

- Powerful immunomodulatory effects but also anti-metastatic and anti-angiogenic effects and are cytostatic and cytotoxic to some tumour cells
- Bind to receptors and signal transduction pathways cause induction of interferon target genes
- Effects on both innate and adaptive immune system
- Used systemically in melanoma, renal cell cancer, HIV-related Kaposi's sarcoma, hairy cell leukaemia, CML and Non-Hodgkins-lymphoma
- Used intra-vesically in TCC bladder
- Toxicities include flu-like symptoms, fatigue and depression

WHAT MONOCLONAL ANTIBODIES ARE IN USE TODAY?

- Herceptin (1998, targets Her-2, used in breast cancer)
- Avastin (2005, targets VEGF itself, used in CRC)
- Erbitux (2006, targets EGFR, mostly humanised, used in CRC and SCC H&N)
- Panitumumab (2007, targets EGFR, fully humanised, used in CRC)
- Many more in development

Key points – chemotherapy

- Docetaxal is a Taxane.
- Vinca alkaloids are highly vesicant.
- Chlorambucil is an alkylating agent that does not characteristically cause alopecia.
- Carboplatin is a non-classical alkylating agent that has a better side effect profile than Cisplatin (which is ototoxic and causes peripheral neuropathy, renal failure). However carboplatin causes marked bone marrow suppression.
- Palma plantar syndrome is an erythematous skin lesion of the palmar and plantar of the hand and feet is most often caused by cytostatic chemotherapy: 5FU is the main culprit.
- Methotrexate is an anti-metabolite that is associated with bone marrow suppression.