Chemotherapy

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Introduction

- Chemotherapy is the use of antineoplastic drugs to promote tumor cell destruction by interfering with cellular function and reproduction
- It includes the use of various chemotherapeutic agents and hormones
- The intent of chemotherapy is to destroy as many tumor cells as possible with minimal effect on healthy cells
- Cancer cells depend on the same mechanisms for cell division that are found in normal cells
- Damage to those mechanisms leads to cell death.

Chemotherapy is utilized in different clinical settings:

- As induction chemotherapy for advanced disease

1. Primary treatment for patients who present with advanced cancer for which no alternative treatment exists

2. As an adjunct to local methods of treatment

-Adjuvant chemotherapy is the use of systemic treatment after the primary tumor has been controlled by surgery and/or radiation therapy

- To palliate symptoms of metastatic disease and/or prolong survival

Chemotherapeutic agents can be effective on one of the four phases of the cell cycle or during any phase of the cell cycle

- G1 (gap one) phase: ribonucleic acid (RNA) and protein synthesis (enzymes for DNA synthesis are manufactured)
- S (synthesis) phase: During a long time period, the DNA component doubles for the chromosomes in preparation for cell division.
- G2 (gap two) phase: This is a short time period; protein and RNA synthesis occurs, and the mitotic spindle apparatus is formed
- M (mitosis) phase: In an extremely short time period, the cell actually divides into two identical daughter cells
- Cells not active in the cell cycle are designated as —resting (G0). Cells in this phase are, for the most part, refractory to chemotherapy.

Therapeutic strategies

1. **Adjuvant therapy:**

- Given to patients who have no evidence of residual disease but who are at high risk for relapse
- The justification for adjuvant chemotherapy is the high recurrence rate after surgery for apparently localized tumors

2. Neoadjuvant therapy (Preoperative chemotherapy):

- Administered prior to surgery in an attempt to downstage the primary tumor so that less invasive surgery can be performed
- For example, patients with large breast tumors can preserve the breast and undergo lumpectomy instead of mastectomy
- The goal of therapy is to decrease the amount of tissue that needs to be removed as well as to attempt to maximize cure potential

3**. High dose/intensive therapy**

- Administration of high doses of chemotherapy, usually in association with growth factor support or before bone marrow transplant/stem cell rescue
- Dose intensification has received increasing emphasis in recent years as a strategy for overcoming resistance to chemotherapy
- Malignant cells may be resistant to certain drugs from the start of therapy (natural resistance) or become resistant after therapy has begun (acquired resistance)
- Dose intensification suggests that chemotherapy should be given in the highest tolerated dose over the briefest interval, with the growth factor support –This has been tested in breast cancer, and results show that it is more effective than standard treatment schedules and is equally tolerated

4. Single agent chemotherapy: use of one cytotoxic drug and is rarely curative as genetically resistant cells are selected out.

5. Combination chemotherapy: use of drug combinations with different mechanisms of actions and side effect profiles which together reduce likelihood of resistance and toxicity. The drugs used should have;

- Cytotoxic activity for that tumour, preferentially able to induce remission
- Different MOAs, ideally additive or synergistic
- Non overlapping toxicity to maximise benefit of full therapeutic doses
- Different mechanisms of resistance.

Routes of administration

- Oral—capsule, tablet, or liquid
- I.V.—push (bolus) or infusion over a specified time period.
- Intramuscular
- Intrathecal/intraventricular—given by injection via an Ommaya reservoir or by lumbar puncture
- Intra-arterial
- Intracavitary—such as peritoneal cavity
- Intravesical—into uterus or bladder
- Topical

- Dosage is based on surface area (mg/m2) in both adults and children
- Most chemotherapeutic agents have dose-limiting toxicities that require nursing interventions
- Chemotherapy predictably affects normal, rapidly growing cells (bone marrow, GI tract lining, hair follicles)
- It is imperative that these toxicities be recognized early on by the nurse

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

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 (Eastern Cooperative Oncology Group)

Karnofsky Perfomance Scale Index

Score, %	State of Health
100	Healthy, no symptoms or signs of disease
90	Capable of normal activity, few symptoms or signs of disease
80	Normal activity with some difficulty, some symptoms or signs
70	Caring for self, not capable of normal activity or work
60	Requiring some help, can take care of most personal requirements
50	Requires help often, requires frequent medical care
40	Disabled, requires special care and help
30	Severely disabled, hospital admission indicated but no risk of death
20	Very ill, urgently requiring admission, requires supportive measures or treatment

WHO/ECOG score

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature—for example, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG, Eastern Cooperative Oncology Group.

Contraindications of chemotherapy

- When facilities are inadequate to evaluate response to monitor and manage toxic reactions
- Patients not likely to survive longer even if tumor shrinkage could be accomplished
- Patient not likely to survive enough to obtain benefits (severely debilitated)
- Patient is asymptomatic with slow growing incurable tumor in which case chemotherapy should be postponed until symptoms require palliation

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

Cytotoxic drugs

How chemotherapy works

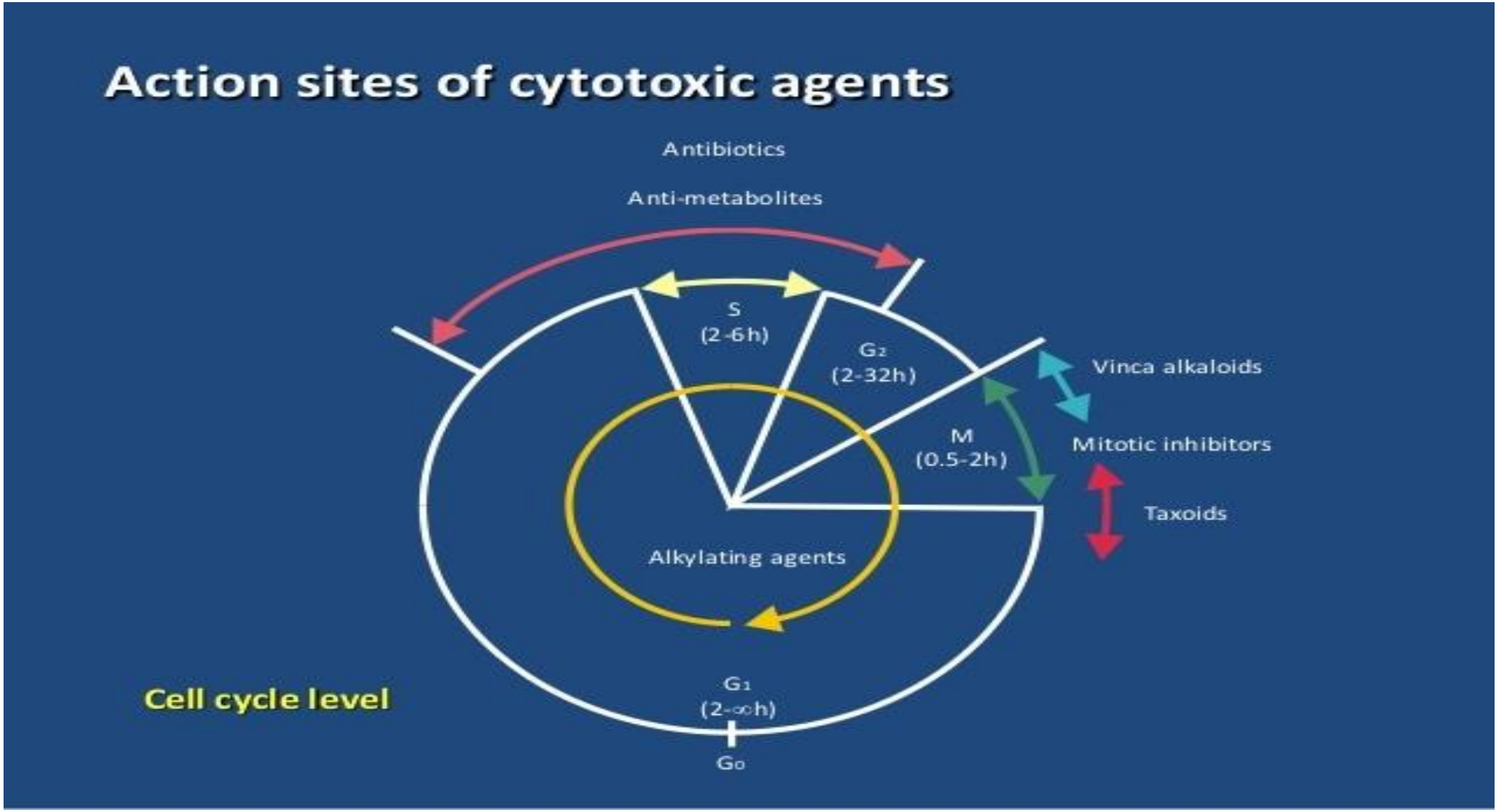
- Tumour cells have poor DNA repair mechanisms
- Normal cells can repair or replace themselves more efficiently
- Intermittent chemotherapy damages **both** normal replicating cells **and** tumour cells but the tumour cells do not recover as quickly
- DNA damage may prevent production of daughter cells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

Classification

Classification of Cytotoxic Agents

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

Action sites of cytotoxic agents



Anti-tumor 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 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

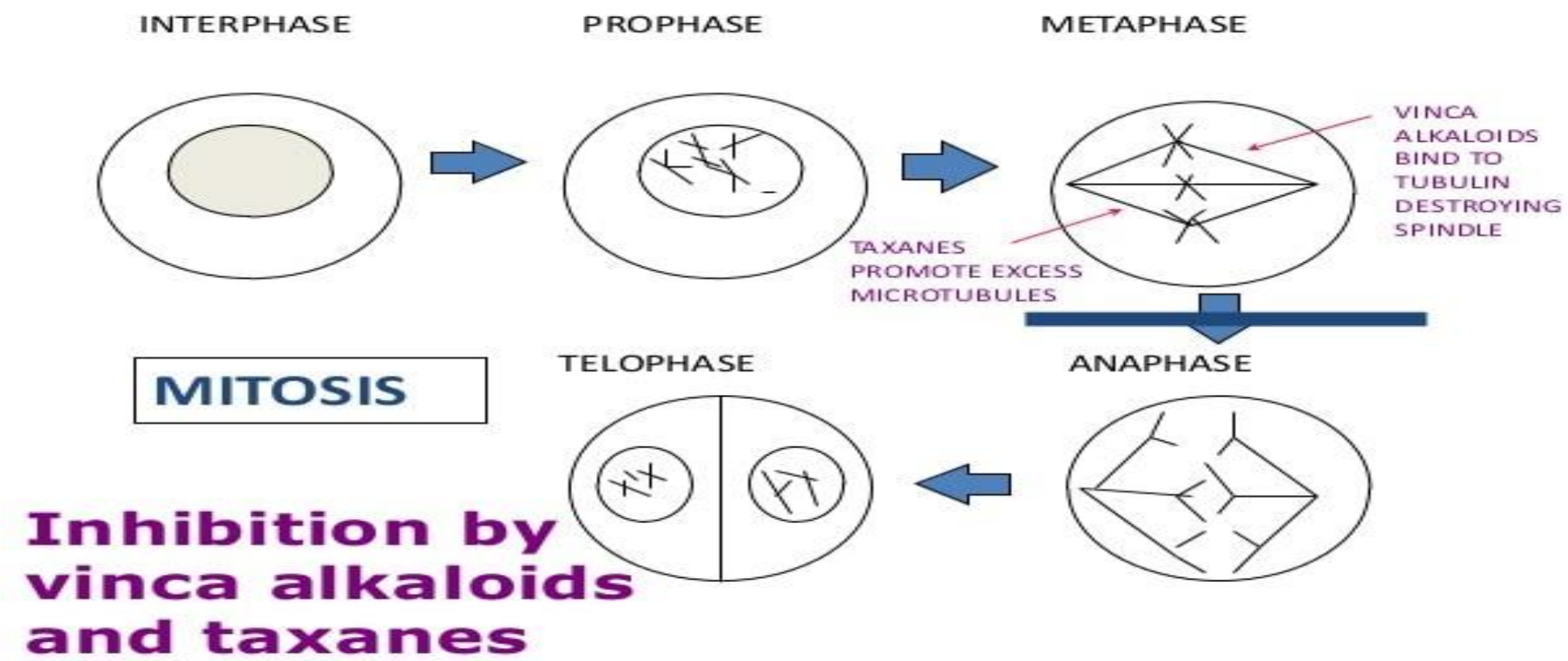
Anti-metabolites

- 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.

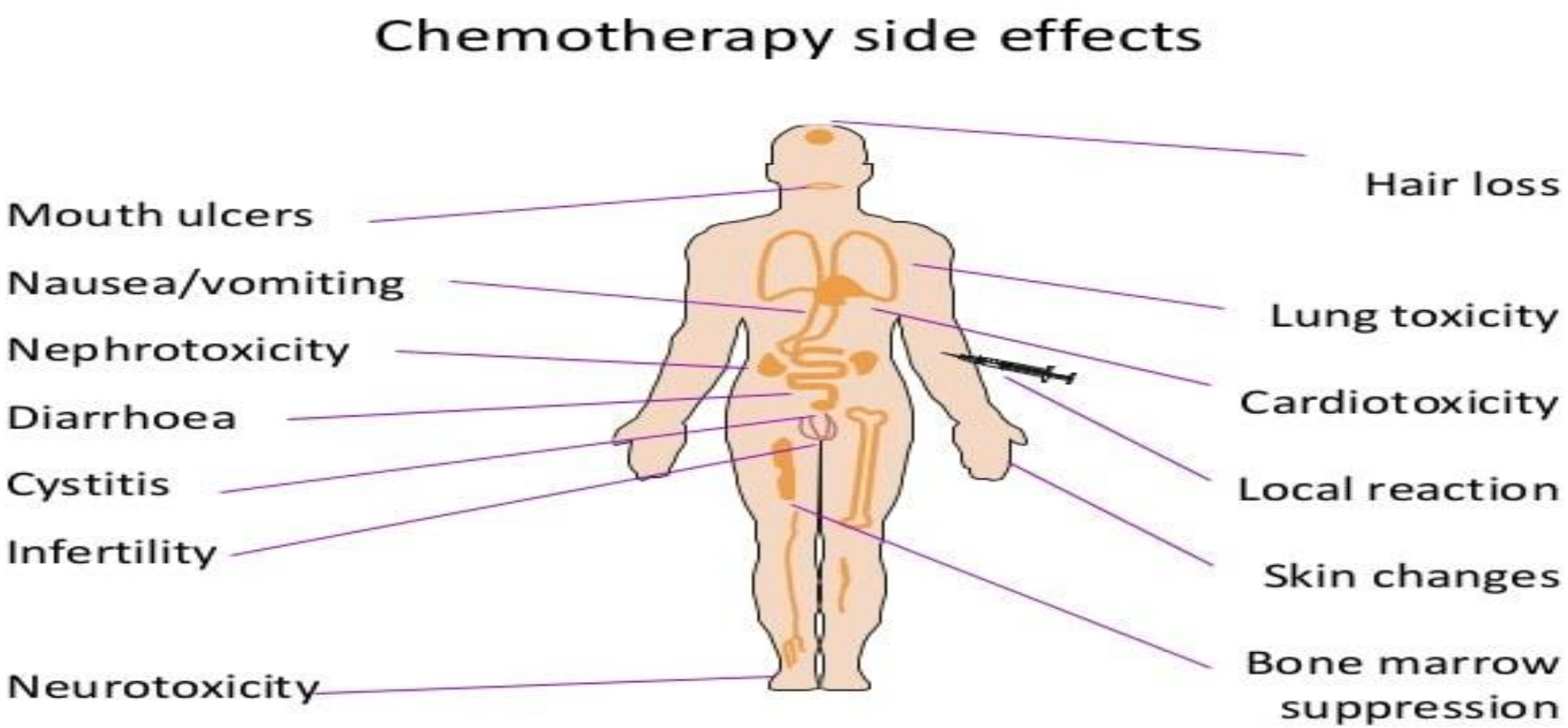
Vinca alkaloids

- 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

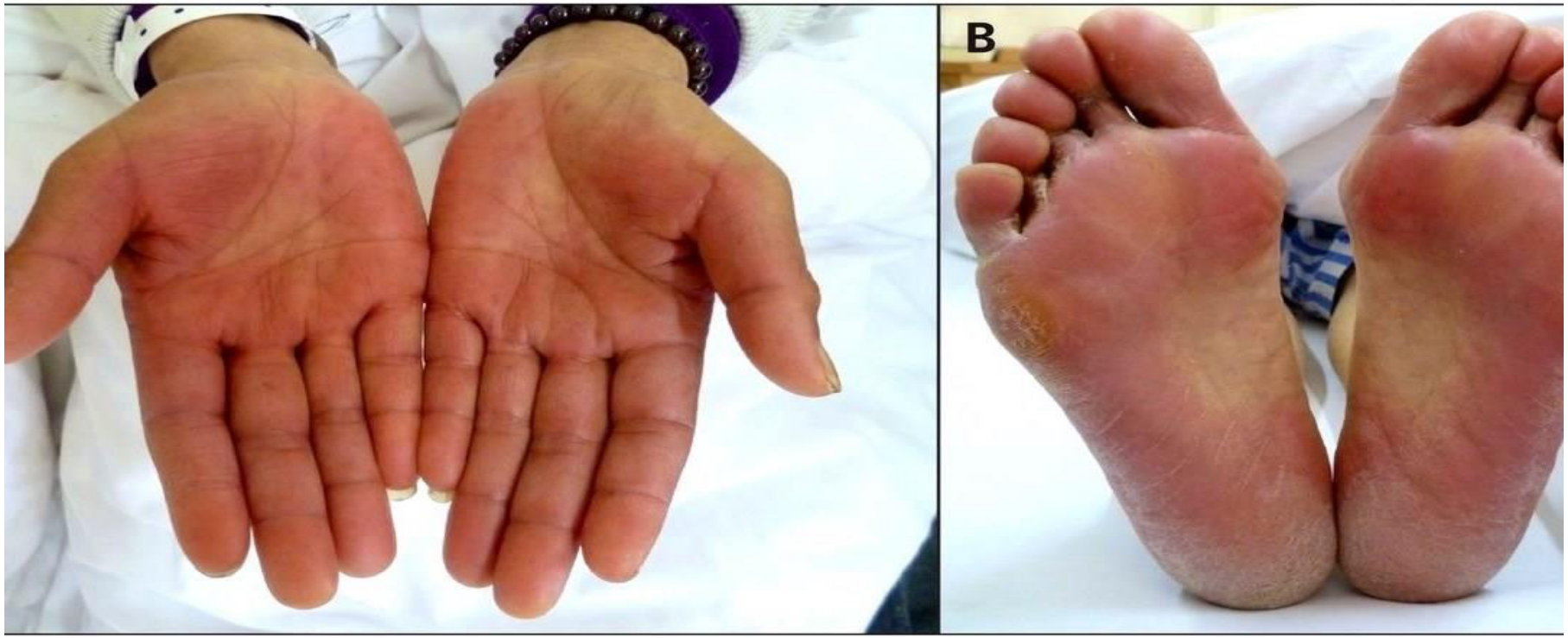
MOA: vinca alkaloids and taxanes



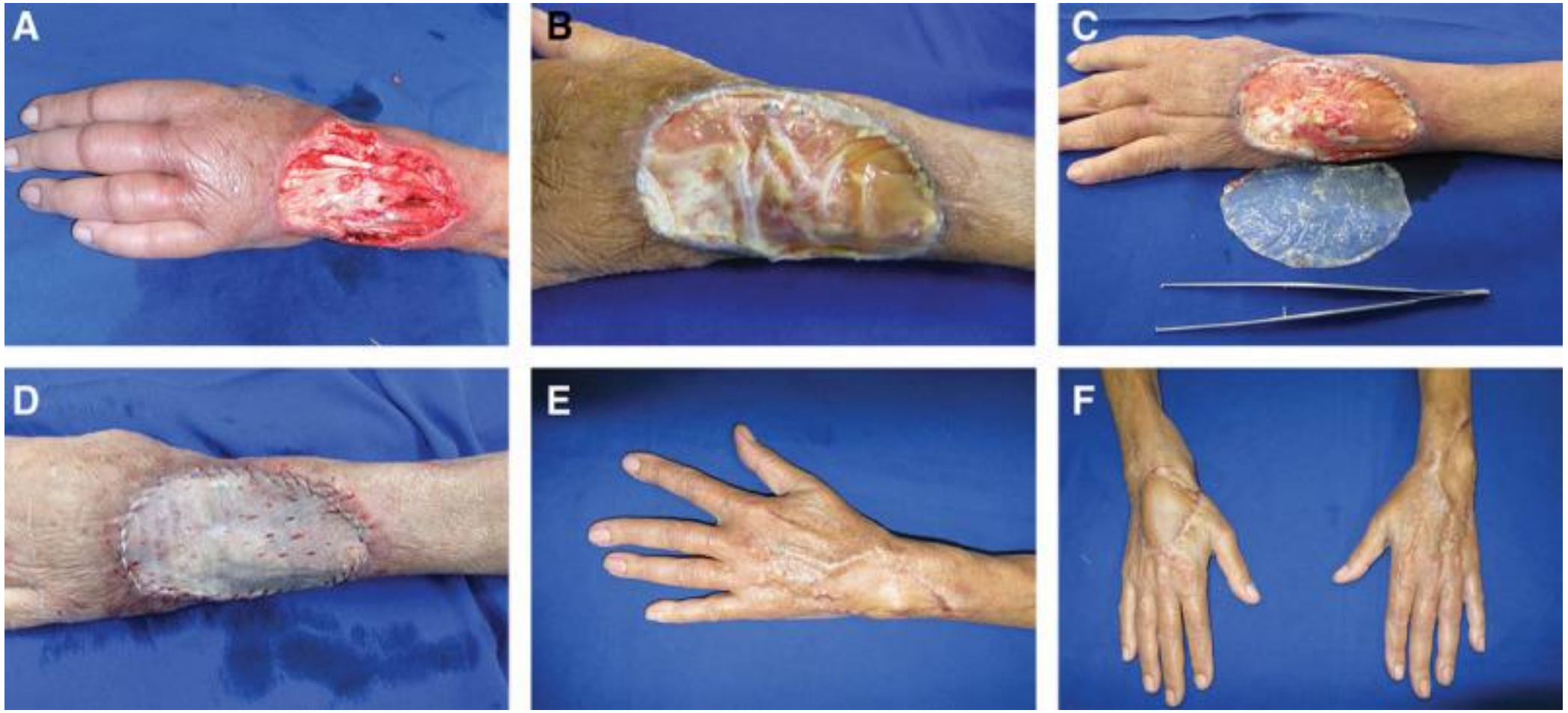
Chemo side effects



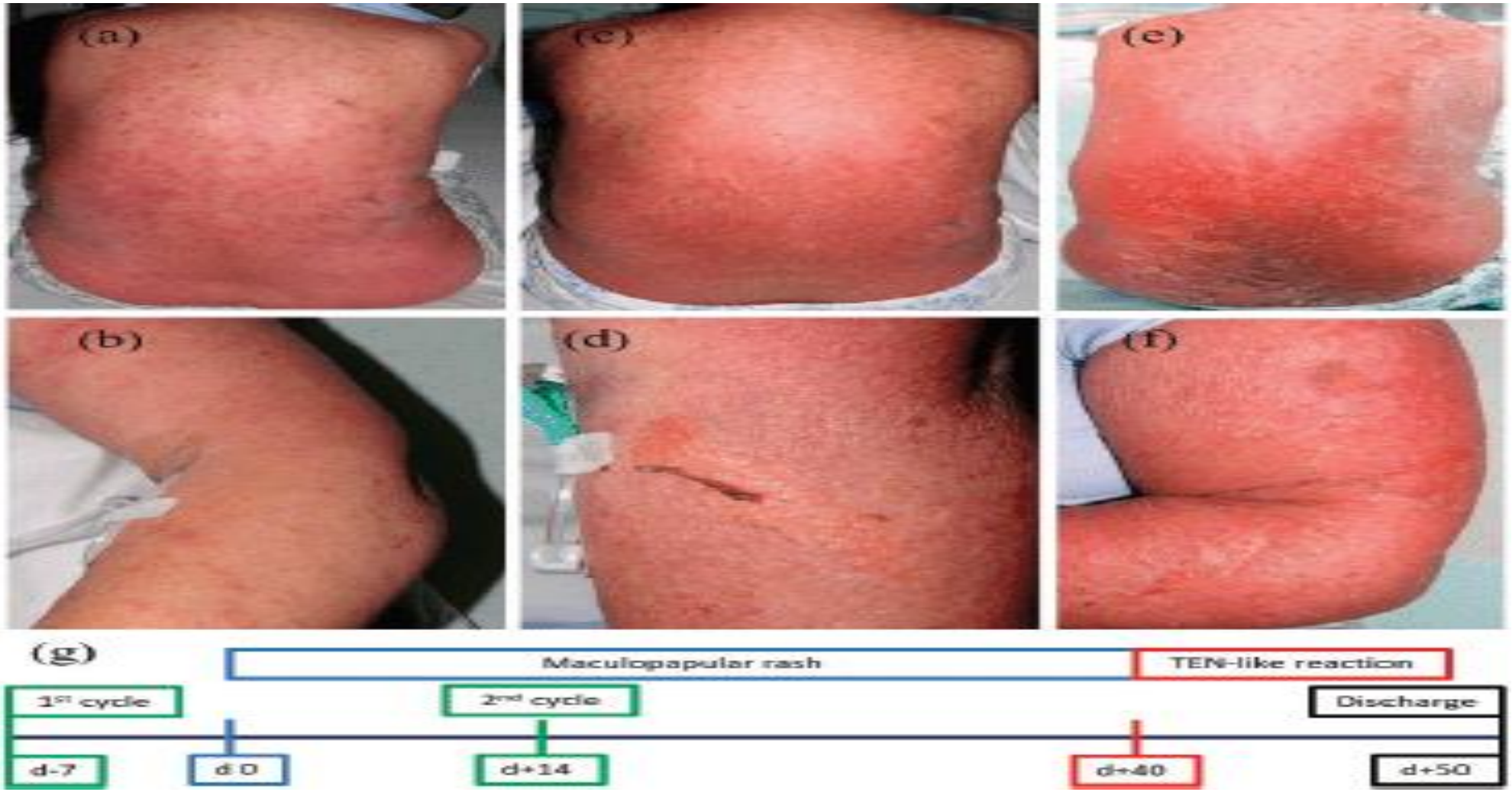
Hand-foot syndrome



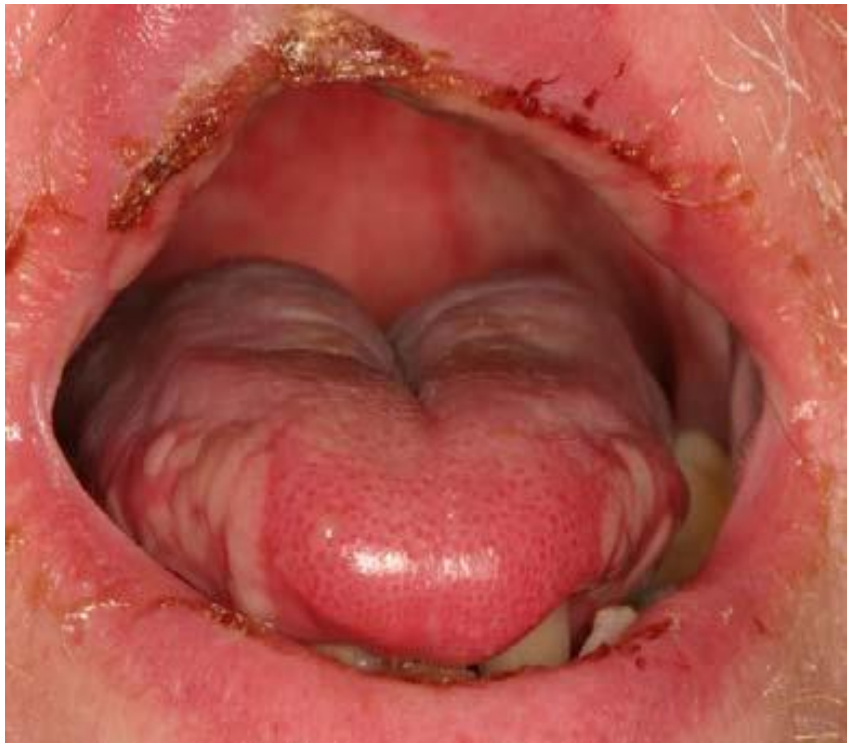
Chemo extravasation

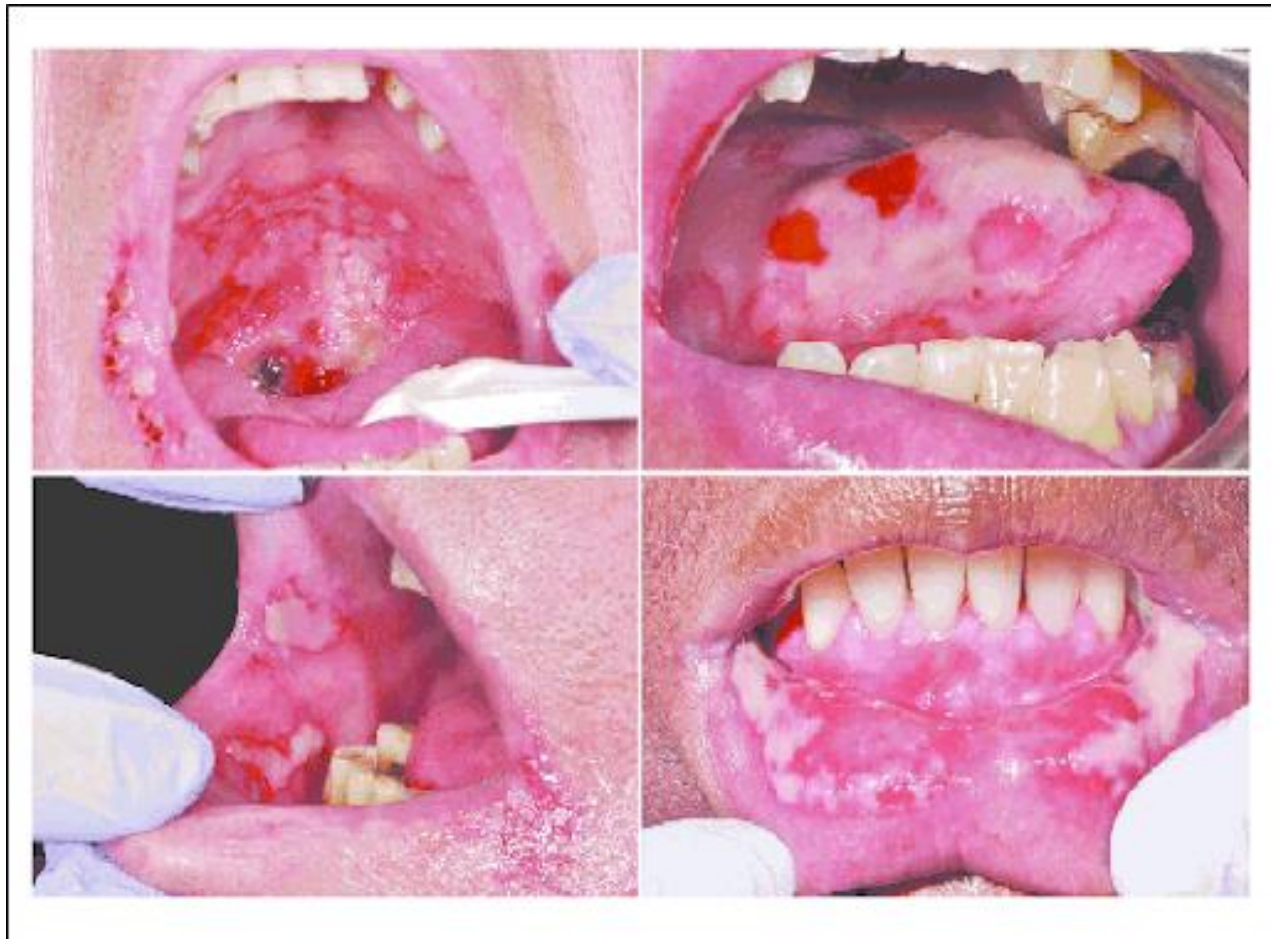


Chemo allergic reaction

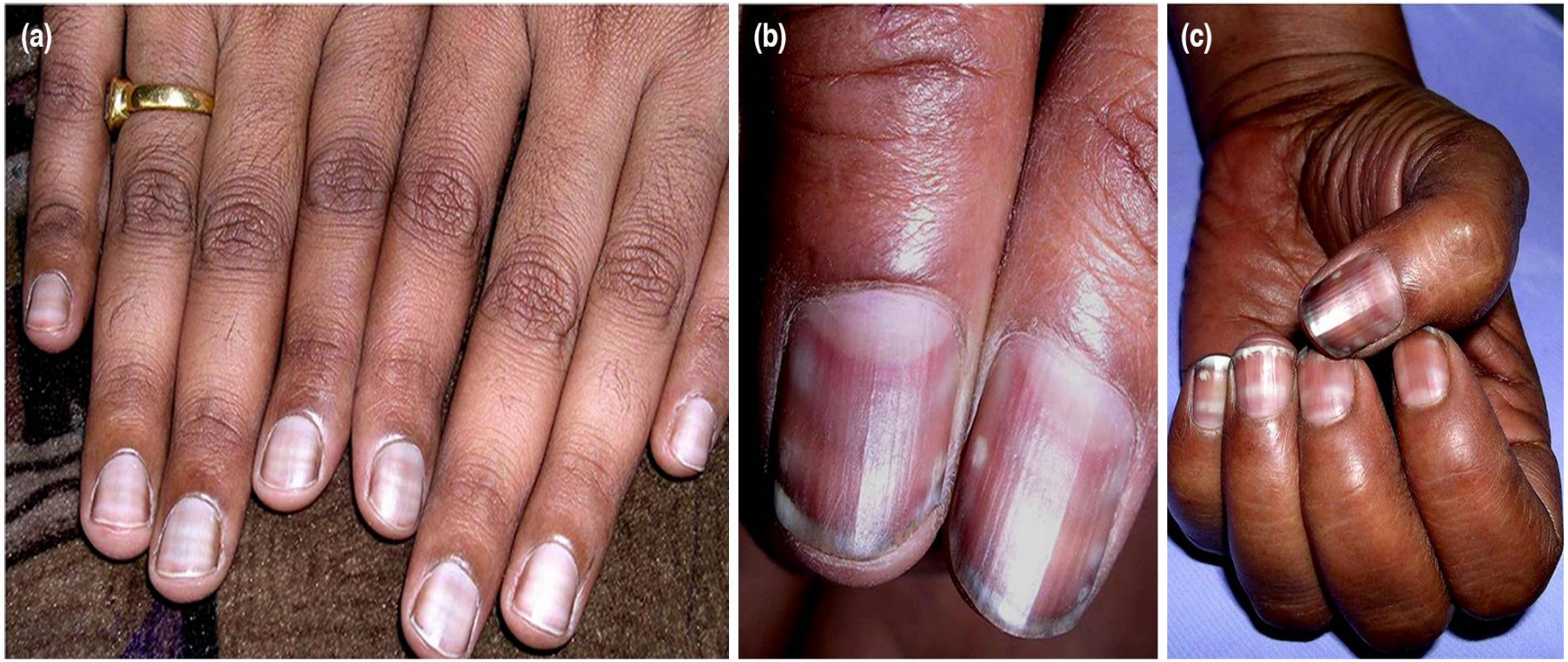


mucosities





Nail changes



Toxicity prevention

- Prophylactic anti-emetics
- Vascular access devises minimise extravasation
- Adequate pre/post hydration, good nutrition, rest
- 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)

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 108 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 tumor is small (less likely to contain resistant cells)
- Use combinations of chemotherapy that are non-cross resistant and have different toxicity profiles: e.g. cisplatin and 5-fluorouracil i.e. alkylating agent to damage DNA and anti-metabolite to prevent DNA synthesis and repair
- Use effective doses of chemotherapy drugs e.g. optimal supportive care to allow maintenance of dose intensity

The End