SNAPSHOT OF TOXICITIES OF CHEMOTHERAPY*

Heena Solanki

Wellington Regional Hospital

OVERVIEW:

- Gastrointestinal (GI) Toxicities
- Haematological Toxicities
- Other Toxicities

1. Cardiotoxicity
2. Pulmonary toxicity
3. Nephrotoxicity
4. Bladder toxicity
5. Skin toxicity

GI TOXICITIES

Chemotherapy Induced Nausea and Vomiting (CINV)

Acute: begins within the first 24 hours, peaks in 4-6 hours.

Delayed (or late): after 24 hours, may last up to 7 days.

Anticipatory: occurs prior to treatment, response based on past experiences. Triggered by various stimuli e. g. smell and sight

Refractory/Breakthrough: inadequate control despite optimal antiemetic therapy.

PATIENT RISK FACTORS

- Female
- Motion sickness
- Migraines
- Pregnancy
- Age
- Anxiety
- High alcohol intake

TREATMENT RISK FACTORS

- **Chemotherapy regimens** e. g. drug, combination and dose.
- **Emetogenicity** of chemotherapy – defined as the risk of emesis in the absence of prophylaxis.
- 4 categories:
  - **High** 90% e. g. **cisplatin, dacarbazine**
  - **Moderate** 30-90% e. g. **doxorubicin, oxaliplatin**
  - **Low** 10-30% e. g. **paclitaxel, bortezomib**
  - **Minimal** < 10% e. g. **pembrolizumab, vincristine**

ANTIEMETIC CLASSIFICATIONS

- 5-HT_3 (serotonin) receptor antagonists e. g. **ondansetron**
- NK_1 (neurokinin-1) receptor antagonists e. g. **aprepitant**
- Corticosteroids e. g. **dexamethasone**
- Antipsychotics e.g. **olanzapine,** haloperidol
- Benzodiazepines e. g. **lorazepam**
- Anticholinergics e. g. **atropine,** hyoscine (scopolamine)
- D_2 (dopamine) receptor antagonists e. g. **domperidone, metoclopramide**
- H_1 (histamine) receptor antagonists e. g. cyclizine and promethazine
- Cannabinoids e.g. nabilone

ANTIEMETIC GUIDELINES

Antiemetic tables

These tables act as a guide to antiemetic therapy. Patient factors, drug interactions and formulation availability should be considered when the medication regimen.

Minimal emetogenic potential

No anti-emetics routinely required. May consider:

MEDICATION	DOSE	FREQUENCY
Metoclopramide	10mg	**Breakthrough:** Three times daily if required

Low emetogenic potential

May consider:

MEDICATION	DOSE	FREQUENCY
Ondansetron	8mg	**Pre-chemo**: 30 to 60 minutes prior to treatment
Olanzapine	5mg	**Breakthrough:** Nightly if required

Moderate emetogenic potential

Medication	DOSE	FREQUENCY
Ondansetron	8mg	**Pre-chemo:** 30 to 60 minutes prior to treatment
		Post-chemo: D1 night
Dexamethasone **Not required if regimen already contains high-dose steroid*	8mg	**Pre-chemo**: 30 to 60 minutes prior to treatment
		Post-chemo: D2-3 once daily
*Metoclopramide *ONLY if dexamethasone contraindicated*	*10mg*	***Pre-chemo**: 30 to 60 minutes prior to treatment*
		***Post-chemo**: D1-5 Three times daily*
Olanzapine	5mg	**Breakthrough**: Nightly if required

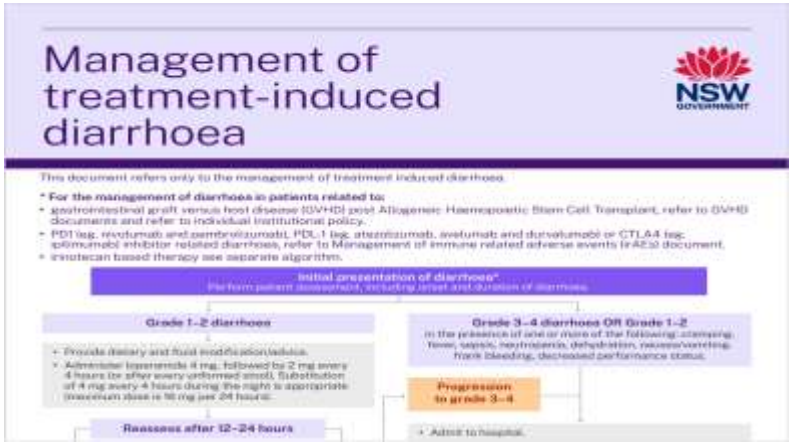
High emetogenic potential

MEDICATION	DOSE	FREQUENCY
Aprepitant **See PHARMAC Special authority criteria.*	Day1: 125mg Day2&3: 80mg	**Pre chemo:** 125mg one hour prior to treatment
		Post chemo: 80mg daily D2-3
Ondansetron	8mg	**Pre-chemo:** 30 to 60 minutes prior to treatment
		Post-chemo: D1 night.
Dexamethasone	8mg	**Pre-chemo**: 30 to 60 minutes prior to treatment
	8mg	**Post-chemo**: D2-3 once daily
Olanzapine	5mg	**Post-chemo**: D 1-4 Nightly
Metoclopramide	10mg	**Breakthrough:** Three times daily if required

Other considerations:

DIARRHOEA

- **Loperamide** - decreases intestinal motility by directly affecting the smooth muscle of the intestine.
- **Atropine** – used as a premedication for **irinotecan** to prevent acute cholinergic syndrome (N +V, diarrhoea, excessive sweating, cramps, etc.)
- **Octreotide** - **second line** therapy for patients who do not respond to high dose loperamide.



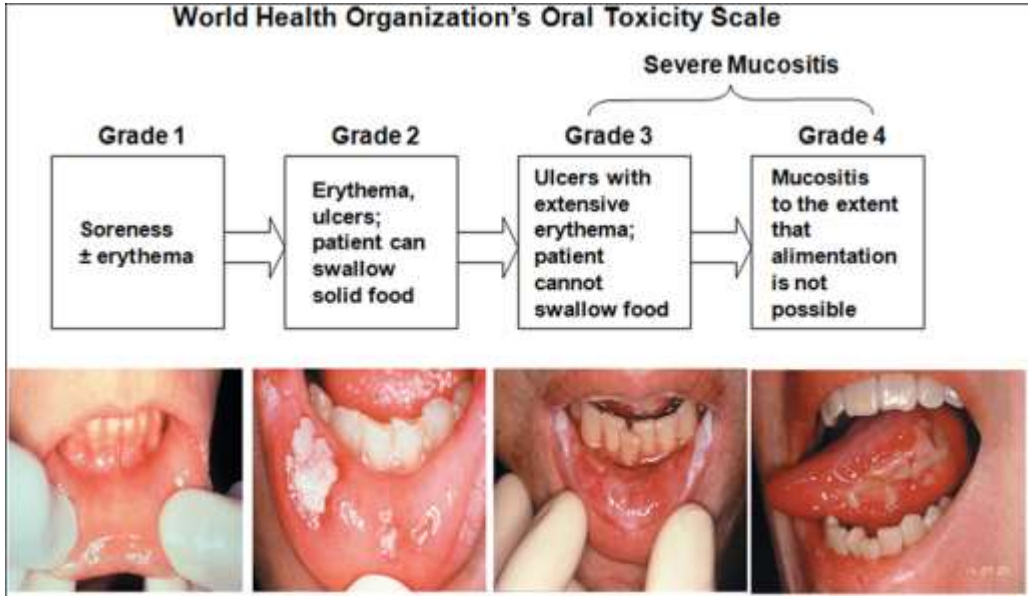
Available from: www.EVIQ.org.au

MUCOSITIS

- Inflammation or damage to mucosa
- GI tract e.g. oral cavity, oesophagus, intestines
  - Incidence 5-20% of patients treated with chemo for solid tumours
  - 60-100% patients on stem cell transplant regimens
  - Up to 100% of patients receiving therapy for head & neck cancer due to RT

MUCOSITIS

- Prevention and treatment
  - Frequent oral assessments
  - Good oral hygiene
  - Patient education and counselling
  - Analgesics
  - Anti-fungal
  - Anti-viral



CARDIOTOXICITY

- Associated with **anthracyclines, fluorouracil, taxanes, TKI's, trastuzumab, arsenic trioxide**
  - Range from **asymptomatic** abnormalities to a **decline LVEF**, **ECG changes** to **life threatening events MI or CHF**

- **Risk Factors:**
  - Age
  - Pre-existing heart disease, concomitant cardiovascular risk factors e.g. **diabetes**
  - Smoking
  - Genetics
  - **Lifetime exposure of anthracycline (> doxorubicin equivalent 450-500mg/m^2)**

- Assessments
  - ECG's, ECHO's

- Management
  - Patient counselling on lifestyle factors, risk of complications from the chemo, monitoring, report any changes in breathing, palpitations, swelling in extremities
  - Dose reduction or stopping therapy
  - Use of cardio protectants i.e. **dexrazoxane**
  - Drug therapy e.g. **ACE inhibitors**

PULMONARY TOXICITY

- Associated with **bleomycin**, carmustine, cytarabine, methotrexate, checkpoint inhibitors e.g. **pembrolizumab**

- Prevention - limiting lifetime exposure to bleomycin, lung function tests
- Risk factors - age, smoking, chronic lung disease
- Management
  - Omit drug e.g. BEP or ABVD regimens
  - Steroids

NEPHROTOXICITY

- Commonly associated with drugs such as **cisplatin**
  - Impair sodium & water reabsorption
  - Interfere with reabsorption of potassium, magnesium and calcium
  - and **Methotrexate** damages the kidney physically
    - Must be dissolved in urine to be excreted
    - Precipitates in acidic environment
- Prevention
  - Pre- and Post-hydration – to ensure adequate urinary output
  - Urine alkalinisation for methotrexate e.g. sodium bicarbonate
- Management
  - Monitor renal function
  - Change cisplatin to carboplatin

BLADDER TOXICITY

- Associated with high doses of ifosfamide and cyclophosphamide
- Haemorrhagic cystitis – diffuse bleeding of the lining of bladder
- Inactive metabolite (acrolein) binds to bladder mucosa and damages bladder wall
- Prevention/Management
  - Hydration –decreases acrolein contact time
  - Mesna –binds to acrolein

NEUROTOXICITY

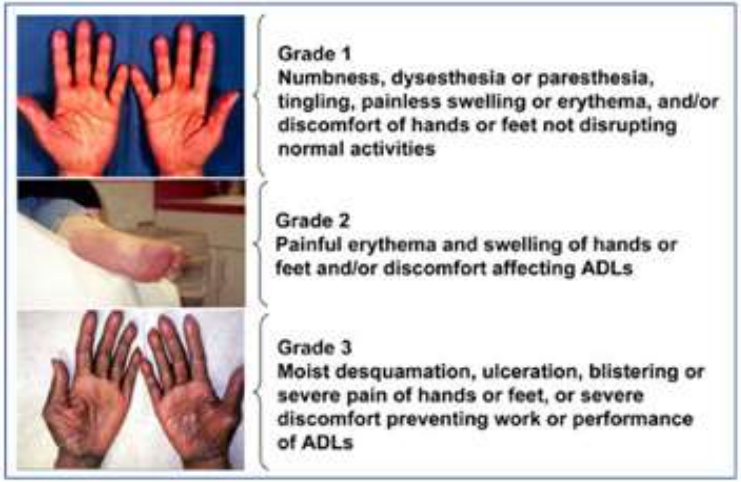
- Commonly associated with **vinca alkaloids,** cytarabine, ifosfamide**, taxanes, oxaliplatin***
- Risk based on dose of drug, multi drug regimen, combination with radiotherapy
- Damage to central and peripheral nervous systems
  - Encephalopathy+
  - Cerebellar syndrome
  - Seizures
  - Peripheral neuropathy, cranial neuropathy
  - Myopathy
- Managed via dose reductions or stop drug

*longer infusion time 2-6 hours (usually prolong it over 3 hours)
+ methylene blue

HAND-FOOT SYNDROME

- Associated with capecitabine
  - Tingling
  - Sore
  - Skin peeling
  - Burning sensation

- Management
  - Stop drug/ dose reduce
  - Hand moisturisers, containing lanolin
  - Analgesics
  - Dermatology referral



HAEMATOLOGICAL TOXICITIES

- Haematopoiesis is blood cell production.
- Your body continually makes new blood cells to replace old ones.
- Haematopoiesis ensures you have a healthy supply of blood cells to supply oxygen to your tissue (**red blood cells**), fight infection (**white blood cells**) and clot your blood when you're injured (**platelets**).
- Causing:
  - **Neutropenia**
  - **Thrombocytopenia**
  - **Anaemia**

NEUTROPENIA

- Reduction in circulating neutrophils in peripheral blood
- Neutrophils
  - 50-75% of all white blood cells
  - Produced from bone marrow over 10-14 days
  - Short lifespan –up to 5.4 days in bloodstream
  - Part of the body's innate immune response, acting as first line of defence against infections.

- **Normal** 1.5 - 7.0 x 10^9/L
- **Mild** 1.0 - 1.5 x 10^9/L
- **Moderate** 0.5 - 1.0 x 10^9/L
- **Severe** Less than 0.5 x 10^9/L

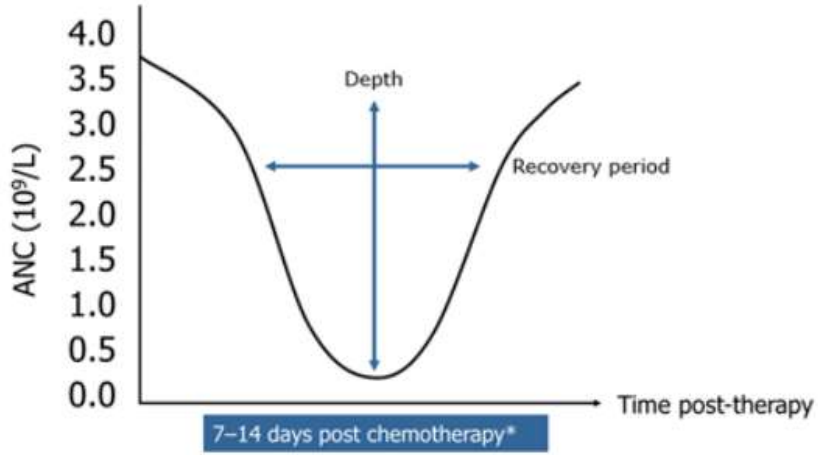
NEUTROPENIA

- Symptoms
  - Fall in neutrophil count is asymptomatic
  - Symptoms are associated with neutropenic complications

- Causes
  - **Disease related**
    - Malignant disease affecting production
  - **Functional**
    - Malignancy results in defects of circulating neutrophils
  - **Chemotherapy induced**
    - Suppression of haematopoietic system by cytotoxic agents
    - Primary cause of **dose reduction** and **treatment delays**
    - Risk of infection

NEUTROPHIL NADIR

- Nadir = lowest ANC (Absolute Neutrophil Count)



THROMBOCYTOPENIA

- Reduced platelet count < 75-150 x 10^9/L
- Normal value 150-400 (450) x 10^9/L
  - Lower for hematological malignancy
  - Patient dependent – risks vs benefits

- Causes:
  - Chemotherapy
  - Viral infections (EBV)
  - Malignancy
  - Congenital/acquired autoimmunity
  - Vitamin B12/Folic acid deficiency

ANAEMIA

- Haemoglobin
  - >80 g/L

  - Identify the cause e.g. disease, nutritional deficiencies, treatment-related
  - Iron supplementation
  - ESA (erythropoiesis stimulating agents)
  - Transfusion therapy
  - Supportive care

MANAGEMENT

- FBC prior to chemotherapy (< 24-48 hours) - usual threshold for chemotherapy to proceed
- Chemotherapy should be delayed until recovery of counts
- Use of GCSF may be considered for subsequent cycles as secondary prophylaxis
- Doses for subsequent cycles may need to be adjusted

FEBRILE NEUTROPENIA

- Neutropenia AND a fever
  - Neutrophils <1 x 10^9/L
  - Fever ≥ 38°C
- Neutropenic sepsis with or without fever is a medical emergency. Other symptoms:
- Altered consciousness
- Hypotension
- Hypothermia
- Signs of organ failure
- Requires prompt administration of IV antibiotics as per local neutropenic sepsis guidelines and pathway
- Delays may cause morbidity and mortality

ANTIMICROBIAL MANAGEMENT

- Follow local guidelines

IV broad spectrum antibiotics: a stat dose within 60 minutes of pathway initiation.

Cefepime 2 g IV infusion q8h (administer over 30 minutes in 100 mL sodium chloride).

- Factors to consider e.g. penicillin allergy, etc.

PREVENTION:

- Goal is to minimise risk of infections and complications

- The three main strategies are:
  - Antibacterial e.g. co-trimoxazole for PJP
  - Antifungal e.g. fluconazole, posaconzole
  - Antiviral e.g. valaciclovir

  - Use of GCSF
  - Environmental precautions e.g. isolated room, infection control, wearing a mask, etc.

QUESTIONS: