Complications of the Systemic Treatment of Cancer

"In the computer model the only side effect was a dry mouth."

An Introduction to Acute Oncology – July 2015
Aims and Objectives

- To be aware of the range of systemic therapies used in modern cancer care
- To list the potential negative effects of these therapies by body system
- To describe the assessment and immediate management of the four most common acute presenting problems
- To know when to seek advice on the management of systemic effects
Overview

- Classification of Systemic Therapies
- Acute and Late Effects
- Acute Effects by Body System
- The Big Four
  - Neutropenic Sepsis
  - Nausea and Vomiting
  - Diarrhoea and Bowel toxicity
  - Skin Toxicity
Systemic Therapies

• Treatment that reaches cells throughout the body by travelling through the bloodstream

  • Radical – primary treatment for specific cancer types e.g.: haematological malignancies
  • Adjuvant – to eliminate micrometastatic spread and increase cure rates after surgical treatment of solid tumours
  • Palliative – to treat disseminated disease
Classification of Systemic Therapies

- **Cytotoxic chemotherapy**
  - Eg: Carboplatin
  - FEC
  - BEACOPP

- **Monoclonal Antibodies**
  - Eg: Trastuzumab
  - Bevacizumab
  - Cetuximab

- **Tyrosine Kinase Inhibitors**
  - Eg: Erlotinib
  - Sunitinib
  - Imatinib

- **Hormones or hormonal blockade**
  - Eg: Tamoxifen
  - Zoladex
  - Provera

**Targeted Therapies**
Acute and Late Effects

Toxicity expression relates to the turnover rate of target tissues
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
- Hepatic
- Haematological
- Circulatory
- Gastrointestinal
- Renal / Urological
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
- Hepatic

Haematological
- Neutropaenia
- Lymphopaenia
- Thrombocytopenia
- Anaemia

Renal / Urological
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
- Hepatic
- Haematological
- Circulatory
  - Hypertension
  - Cardiac Failure
  - Emboli
- Renal / Urological
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
- Hepatic
- Haematological
- Circulatory
- Gastrointestinal
  - Nausea and Vomiting
  - Diarrhoea
  - Constipation
  - Reflux
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
- Hepatic
- Haematological
- Circulatory
- Renal Impairment
  - Cystitis
  - Electrolyte loss
- Renal / Urological
Acute Effects

- Nervous System (Central and Peripheral)
- Haematological
- Skin and Hair
- Circulatory
- Respiratory
- Gastrointestinal
- Hepatic
- Renal / Urological
- Hepatitis
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
- Respiratory
  - Pneumonitis (bleomycin)
- Haematological
- Circulatory
- Gastrointestinal
- Renal / Urological
Acute Effects

- Nervous System (Central and Peripheral)
- Skin and Hair
  - Hair Loss
  - Acne-like rash
  - Peeling/Cracked skin
  - Altered pigmentation
- Hepatic
- Haematological
- Circulatory
- Gastrointestinal
- Renal / Urological

Hair Loss
Acne-like rash
Peeling/Cracked skin
Altered pigmentation
Acute Effects

Nervous System (Central and Peripheral)
- Nausea and Vomiting
- Encephalitis
- Peripheral neuropathy
- Laryngospasm
- Fatigue

Haematological

Circulatory

Gastrointestinal

Renal / Urological

Hepatic

Fatigue
The Big Four

• Neutropenic Sepsis
• Nausea and Vomiting
• Diarrhoea and Bowel toxicity
• Skin Toxicity
Neutropenic Sepsis

• Cytotoxics and some small molecule drugs cause reduced blood cell counts

• Neutrophil nadir typically 7-10 days post treatment but can occur at any point in cycle

• Causes reduced resistance to infection especially by bacteria
Neutropenia – < 1 x 10⁹/L

- Neutropenic sepsis
  - A significant inflammatory response to bacterial infection in a person with low neutrophil count +/− fever
  - Neuts < 1 x 10⁹ AND fever >38 OR unexplained clinical deterioration

- Severe Sepsis
  - Sepsis as above PLUS evidence of organ dysfunction, hypotension or poor perfusion

- Septic Shock
  - Severe sepsis as above PLUS hypotension not responding adequately to fluid resuscitation
Neutropenic Sepsis – Risk Groups

- A history of fever OR feeling unwell in:
  - Any patient within 6 weeks of chemo
  - Any patient within 1 year of high dose chemotherapy or bone marrow transplant

- Heavily pre-treated
- Previous episodes
- Mucosal / skin breakdown
- Comorbidity
- Elderly
- Haematological primary
Neut Sepsis - Assessment

• History
  • Regime, date of last cycle
  • Infective symptoms – systems review
  • Current or recent antibiotic use, Comorbidity

• Examination
  • SHEWS – pulse, BP, RR, Temp, Sats etc.
  • Skin – rash, pallor, mottling, cap refill
  • Mental status and Systemic exam
  • Lines and Cannula site
  • DO NOT PR
Action – The Red Pathway

- To ensure prompt treatment of neutropenic patients with, or at high risk of developing severe sepsis – started BEFORE neutrophil count known

- Urgent: FBC, Cx, UE, LFT, Clotting, Lactate, Glu, CRP
- Cannulate and administer iv antibiotics as per local protocol WITHIN 1 hour, DO NOT WAIT for neutrophil count
- Assess need for ivi
  - Consider fluid challenge if BP <90
  - Commence fluid balance and monitor U.Output
- Assess for O2 therapy aiming Sats>94%
- Send appropriate specimens (MSU, Site swabs etc.)
- Call for help!
Antibiotic Therapy

- Standard: Tazocin 4.5g iv qds + gentamycin 5mg/kg od

- Penicillin Allergy
  - Ciprofloxacin 500mg bd po PLUS
  - Teicoplanin 400mg iv bd then od

- Suspected central line infection
  - Tazocin PLUS Teicoplanin

- Previous Tazocin-Resistant Organism
  - Meropenem 1g iv tds

- Mucositis
  - Add fluconazole 50mg po
Further Treatment

- Consider Early Discussion with ITU/Outreach if:
  - Patient not improving/ is worsening (evidence of organ dysfunction)
  - BP does not respond adequately to fluid bolus
  - Serum lactate >4 mmol/L

- GCSF – if evidence of organ dysfunction
- Close monitoring – SHEWS, daily review
- Daily FBC, UE, LFT
If Not Improving

- Consider switch of antibiotic or addition of line-cover agent if not already
  - Review culture results
  - Local protocols +/- microbiology advice

- Consider atypical infecting organisms eg: fungi, PCP or viruses
  - Usually only if prolonged neutropaenia (>2-3 weeks) or impaired cell mediated immunity
  - May require CXR/ HRCT or BAL
Action – The Amber Pathway

- Less intensive Rx for those at low risk of severe sepsis
- A history of fever OR feeling unwell within 6 weeks of chemo, BUT
  - SHEWS 0-1
  - No signs of severe sepsis
  - No high risk features
- Oral antibiotics: Co-amoxiclav and Ciprofloxacin +/- early discharge
- Requiring IVI
- CVAD in situ
- Infected PICC line
- Wound or severe soft tissue infection
- Any antibiotic use (inc prophylaxis) in last 72 hrs
- On GSCF
- Poor performance status
- Co-existing medical problem requiring inpatient management
- Pneumonia
- COPD
- HIV +ve
- Pregnancy/Lactation
- Haematology patient

BP < 90
Poor perfusion
Altered mental state
O2 sats < 94%
Urine output < 30mls/hr
Abnormal clotting
Neutropenic Sepsis - Prevention

- Prophylactic GCSF – Days 5-10
  - From first cycle with some regimes (eg TAC)
  - After an episode of neutropenic sepsis

- Prophylactic antibiotics
  - Quinolone +/- fluconazole

- Dose reduction
Nausea and Vomiting

• Common cause of morbidity, prolonged hospital stay, and re-admission

• Cancer nausea and vomiting often multifactorial
  • Systemic therapies, RT, direct or indirect cancer effects, analgesics

• Requires history to establish most likely cause to allow effective management
N&V - Mechanisms

- Acute onset mins to hours post therapy
- Delayed onset >24 hours post therapy
- Anticipatory onset prior to administration
N&V – Systemic Therapy

Direct Drug Effects
- Direct effect on chemoreceptor trigger zone
- Mediated by Serotonin (5HT3), Dopamine (D2), and neurokinin
- Rx: Ondansetron, Domperidone, Aprepitant, Dexamethasone

GI Effects
- Gastric irritation/reflux, gastric stasis and distension, small bowel oedema
- Mediated via Dopamine (D2) receptors
- Rx: Domperidone, Metoclopramide, Haloperidol

Higher Cerebral Effects
- Anxiety, Fear, Memory/Anticipation, Sight, Smell, Taste
- Multiple pathways inc. serotonin, GABA, Histamine (H2)
- Lorazepam, Haloperidol, Levomepromazine, Non-pharmacological
N&V – Emetogenicity

High >90%
- Cisplatin
- Carmustine
- Dacarbazine
- Dactinomycin

Moderate 30-90%
- Carboplatin
- Cyclophosphamide
- Doxorubicin
- Epirubicin
- Oxaliplatin
- Ifosfamide
- Irinotecan
- Paclitaxel
- Docetaxel
- Topotecan
- Etoposide
- Gemcitabine
- Fluorouracil
- Pemetrexed
- Methotrexate
- Cetuximab
- Trastuzumab

Low 10-30%
- Vinorelbine
- Vincristine
- Bleomycin
- Busulphan
- Fludarabine
- Bevacizumab

Minimal <10%
- Bleomycin
- Vinorelbine
- Fludarabine
- Bevacizumab
N&V- Prophylaxis

• Varies according to emetogenicity of individual drugs, doses used and drug combinations

• Low/Moderate:
  • Iv Granisetron pre-med (5HT3 antagonist at CTZ)
  • Po Dexamethasone 4mg bd for 3/7 (?acts at CTZ)
  • Po Domperidone 10-20mg tds for 3/7 then prn (CTZ and gastric)

• High:
  • As above plus Ondansetron 4mg bd for 5/7 (oral 5HT3 antagonist)
  • Or Aprepitant (neurokinin antagonist) premed and od for 2/7 post chemo
N&V Assessment

- **History**
  - Onset in relation to treatment and triggers
  - Use of antiemetics and any response
  - Ability to tolerate food and fluids
  - Frequency of vomiting

- **Examine**
  - BP, Pulse, Cap refill
  - Signs of dehydration
  - Evidence of other causes eg bowel obstruction / UTI etc.

- **Investigate**
  - UE, Bone profile, LFT, FBC
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<thead>
<tr>
<th>Grade</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>Loss of appetite</td>
<td>Decreased intake without weight loss</td>
<td>Insufficient intake, IVI &gt; 24 hours</td>
<td>Life-threatening consequences</td>
<td>Death</td>
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<td></td>
<td></td>
<td>IVI &lt; 24 hours</td>
<td>IVI or TPN</td>
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<tr>
<td>Vomiting</td>
<td>1 per 24 hours</td>
<td>2-5 per 24 hrs</td>
<td>≥ 6 per 24 hrs</td>
<td>Life-threatening consequences</td>
<td>Death</td>
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<tr>
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N&V Treatment

- Prescribe regular antiemetic
- Escalate up the prophylaxis tree
- Trial an agent with a different mechanism of action – target to likely cause
- Consider syringe driver +- ivi support
  - Cyclizine, Levomepromazine, Haloperidol
- Escalate / adjust prophylaxis next cycle
Bowel Toxicity

Constipation
- Vincristine
- Vinblastine
- (5HT3 antagonists)

Diarrhoea
- 5-Fluorouracil
- Capecitabine
- Irinotecan
Diarrhoea - Mechanisms

- **Malabsorption**
  - Loss of intestinal mucosal cells due to cytotoxic effects (rapid cell division)
  - Mucosal integrity lost and impairs absorptive functions – mainly small bowel
  - Increased volumes pass through unabsorbed as diarrhoea

- **Direct Cholinergic Effects on bowel (Irinotecan)**
  - Increased Autonomic nervous system stimulation
Diarrhoea - Assessment

- History
  - Onset, duration, unwell contacts
  - Frequency of stools - ? Nocturnal
  - Nature of stool – watery / bloody

- Examine
  - Pulse, BP, Temp, signs of dehydration
  - Abdominal distension/ obstruction/ tenderness

- Investigate
  - FBC, UE, CRP
  - Stool MC&S and C.Diff Toxin
# Common Toxicity Criteria - CTC

<table>
<thead>
<tr>
<th>Toxicity</th>
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<th>2</th>
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<tbody>
<tr>
<td>Diarrhoea</td>
<td>Increase &lt;4 stools per 24hrs</td>
<td>Increase 4-6 stools ivi &lt; 24 hrs Nocturnal</td>
<td>Increase ≥ 7 stools Ivi &gt;24 hrs Hospitalisation Incontinence Interference with ADL</td>
<td>Life-threatening eg: shock</td>
<td>Death</td>
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Diarrhoea - Treatment

• **General**
  - Clear fluids / low residue diet (BRAT)
  - Ivi support may be required
  - Antispasmodics if needed / antibiotics if indicated

• **Anti-diarrhoeal**
  - Loperamide (4mg → 2mg after each loose stool)
  - Dihydrocodeine
  - Octreotide

• Consider modification of future cycles if severe (G2 or greater)
Treatment – Irinotecan

• Early - during /< 24 hours of therapy
  • Profuse watery diarrhoea associated with flushing, abdominal cramps, dizziness
  • Cholinergic stimulation of bowel motility
  • Px: s/c atropine 300mg as prophylaxis pre-Rx
  • Rx: Repeat atropine dose if symptoms occur

• Late – onset > 24 hours from therapy
  • Mucosal effects but potential to be SEVERE
  • Rx: high dose loperamide (4mg → 2mg 2hourly until 12 hours free of diarrhoea)
Skin Toxicity

- Rarely causes admission, but a major source of morbidity and quality of life impact for some therapy regimes – cosmesis and function

- Can be seen with both cytotoxic and targeted therapies

- Management strategies mostly generic – skin protection and emollients
  - specific measures available for some drugs
  - Worth taking advice if anything more than mild
Skin Toxicity – Cytotoxics

• Palmoplantar Erythema

• Culprits
  • Capecitabine
  • 5-Fluorouracil
  • Caelyx

• Management
  • Emollients
  • Keeping skin dry
  • Dose reduction
  • (Pyridoxine)
Skin Toxicity – Targeted Therapies

• Drugs targeted to EGFR
  • Epidermal Growth Factor Pathway eg: Gefitinib

• Acneiform rash on face, trunk and back

• Management
  • Emollients
  • Sun protection
  • Topical clindamycin
  • Topical steroid
  • Oral doxycycline or minocycline
  • Dose reduction/treatment delay
# CTC - Skin

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<tr>
<td><strong>PPE</strong></td>
<td>Erythema only</td>
<td>Blisters, peeling or pain, not interfering with function</td>
<td>Ulceration, or pain interfering with function</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td><strong>Rash</strong></td>
<td>Mild rash without symptoms</td>
<td>Symptomatic Rash, or desquamation &lt; 50% BSA</td>
<td>Generalised erythroderma, vesicles or Desquamation &gt;50% BSA</td>
<td>Generalised Ulcerative or bullous dermatitis</td>
<td>Death!</td>
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Summary

- Systemic therapies can have unwanted effects on all body systems
- Potential risk to life as well as negative impact on quality
- Neutropenic sepsis should always be discussed with Oncology team
- Other toxicity worth discussing if more than mild – two way communication
Questions?