Side effects of Targeted Therapy

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Cytotoxic Drugs (Chemotherapy)

- Antibiotics
- Antimetabolites
- Alkylating agents
- Vinca Alkaloids
- Anthracyclines

Biological Therapies

- Hormone therapies
  - Goserelin/Zoladex®
  - Tamoxifen

- Monoclonal Antibodies
  - Herceptin
  - Retuximab
  - Bevacizumab (avastin)

- Cancer growth inhibitors
  - Tyrosine Kinase Inhibitors
  - Proteasome inhibitors
  - mTOR inhibitors
  - PI3K inhibitors
  - Histone deacetylase inhibitors
  - Hedgehog pathway blockers

- Pro cytotoxic Drugs
  - Capecitabine

Ongoing research

- Anti cancer vaccines
- Blood cell growth factors
- Blood vessel growth blockers
- IFN/IL2
- Gene therapy
- Radioactive substance carriers (conjugated MABs)
- Drug carriers

Ongoing research
Tyrosine Kinase Inhibitors

• How many do you know!!!!!
TKIs

- Afatanib
- Axitinib
- Bosutinib
- Crizotinib
- Dabrafenib
- Dasatinib
- Erlotinib
- Gefitinib
- Imatinib
- Lapatinib
- Nilotinib
- Pazopanib
- Regorafenib
- Sorafenib
- Sunitinib
- Trametinib
Principles

• Growth factor receptors play a role on the normal processes of cell growth and development.
  – In some cancers these growth receptors are over-expressed leading to unregulated cell growth.
• Molecular pathways involved in cancer cell proliferation are identified
• Drugs are developed to act on these pathways
Symptom grading

• Standardised assessment – objective
  – My small and your small may be different!
• Effective communication and documentation
• Accurate evaluation of new treatments in research
• Make decisions about treatment
  – Continue, dose reduce, stop
• Decisions about effectiveness of symptom management
• How useful are these statements for decision making
  – Patient had a small amount of diarrhoea today
  – Patient vomited ++++
• **Grade 1: Mild;** asymptomatic or mild symptoms; clinical observations only; intervention not indicated

• **Grade 2 Moderate;** minimal, local or non-invasive intervention indicated
• **Grade 3 Severe;**
  medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization

• **Grade 4 Life-threatening consequences; urgent intervention indicated.**
Side Effects of Targeted Therapy

Hair

Endocrine

Cardiovascular

Mouth

Skin

Gastro-intestinal
Hair Changes – Presentation

• Hair Thinning
• Hair may become more brittle.
• Sunitinib & Pazopanib causes loss of pigmentation while taking. Pigmentation can come back during treatment breaks.
Hair changes – Management

• Use mild shampoo

• Use herbal rather than peroxide based hair dyes; if possible use in between treatment cycles and test first.
Oral toxicities – Presentation

• Mucositis - different to chemotherapy induced mucositis
• Irritation of nerve endings
• Can be painful without any visible changes or ulceration
• May extend throughout the gastrointestinal tract

• Taste changes/dysgeusia
Oral toxicity – grading

Oral Mucositis

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
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</table>

Dysgeusia

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<td>Altered taste but no change in diet</td>
<td>Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste</td>
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<td>-</td>
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</table>
Oral toxicity – Management

• Good oral hygiene, including regular visits to the dentist
• Use of soft or baby toothpastes and brushes
• Use of non-alcoholic mouthwashes (commercial mouthwashes are often too astringent)
• Pain and comfort management
  – Analgesia, including analgesic mouthwashes
  – Artificial saliva for dry mouth
  – Lip creams/balms, Gelclear, Bonjela, frozen pineapple chunks
• Diet modification, e.g. avoid hot, spicy, acidic foods; eat little and often
• Keep drinks cool and fluid intake high
• Eat with a spoon rather than a fork; drink using a straw
Skin Toxicity – Presentation

Presentation varies between drugs

- Acneform rash
- Maculopapular Rash
- Xerosis (dry skin)
- Palmar-plantar/Hand-foot syndrome
- Nail discolouration
- Pruritis
- Photosensitivity
- Warty lesions
- Squamous Cell Carcinomas

Patients may also experience allergic skin reactions upon starting therapy and treatment will need to be discontinued.
Acneform Rash

Mild

Moderate

Severe
Acneform Rash

- Develops about 8 to 10 days after the start of treatment
- The occurrence of rash may be intermittent
- Should not be treated as acne
  and over the counter acne treatments may worsen the rash
Maculo-papular Rash – Presentation

- Can present at any time but often improves after the first two cycles of treatment
Pruritis – Presentation & Grading

- Usually occurs with rash but can occur without rash.

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<td>Mild or localized; topical intervention indicated</td>
<td>Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, oozing/crysts); oral intervention indicated; Limiting instrumental ADL</td>
<td>Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</td>
<td>-</td>
</tr>
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</table>
Skin Rash – Management

- Emollient creams to maintain skin hydration
- Use gentle soaps
- Avoid heat - use tepid water when bathing and keep cool in hot weather
- Avoid direct sunlight and use a high SPF sun cream in very sunny weather
- Anti-dandruff shampoos may relieve scalp itching
- Steroid creams or systemic steroids can be used temporarily
- Antibiotics may be required for pustular rashes
- Make-up can be used but brands for sensitive skin are recommended.
Skin lesions

• Specific to vemurafenib & dabrafenib
• Warty protrusions may fall off or subside as treatment progresses.
• If in an awkward place or bleeding refer to dermatology for removal.
Skin lesions

Squamous Cell Carcinoma
Hand & Foot Syndrome – Presentation

• Also known as Palmer Plantar Erythema or Palmar Plantar Hyperkeratosis
• Can be caused by traditional chemotherapies as well as some TKIs
• Can occur at every cycle or on occasional cycles
• Appears at pressure points
Hand & Foot Syndrome – Presentation
Hand & Foot Syndrome – Grading

Palmar-plantar erythrodysesthesia syndrome

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<td>Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain</td>
<td>Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL</td>
<td>Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL</td>
<td>-</td>
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Hand & Foot Syndrome – Management

- Keep skin well moisturised with emollient cream.
- Protect against irritants, e.g. use gloves when washing up.
- Avoid exposure to sun or excessively hot water.
- Keep feet bare whenever possible, or wear cotton socks and low-heeled, soft, snug-fitting shoes.
- Use pressure-relieving pads/gel inserts (particularly soothing if kept in the fridge).
- Keep skin cool when possible.
- Leave blistered skin to heal.
Photosensitivity – Presentation

- Specific to Vemurafenib & Dabrafenib
- More severe with vemurafenib
- A few minutes of sun exposure can result in severe burning or blistering
Photosensitivity – Management

• Prevent by using high SPF suncream, clothing and shade
• Treat with emollients or aloe vera gel
Hypothyroidism

• Specific to Sunitinib and thyroid function monitored at every cycle.
  – However present in the general population so may be picked up if patients on other therapies are screened.

• All patients taking Sunitinib will eventually need thyroxine treatment.

• Monitor for symptoms: fatigue, feeling cold, oedema.
## Diarrhoea

<table>
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<tr>
<th>Patients without colostomy</th>
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<tr>
<td>Increase of less than 4 stools a day compared with pre treatment</td>
<td>Increase of 4 – 6 stools a day or nocturnal stools</td>
<td>Increase of 7 or more stools a day or incontinence, or symptoms of dehydration, abdominal cramping</td>
<td>Over 10 episodes a day or bloody diarrhoea or symptoms of dehydration or haemodynamic instability</td>
<td></td>
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<th>Patients with a colostomy</th>
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<td>Mild increase in loose watery colostomy output compared with pre treatment</td>
<td>Moderate increase in loose watery colostomy output but not interfering with normal activity</td>
<td>Severe increase in loose, watery colostomy output interfering with normal activity, abdominal cramping</td>
<td>Severe increase in loose, watery colostomy output and/or symptoms of dehydration or haemodynamic instability</td>
<td></td>
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Diarrhoea

- Severe or persistent
  - Dehydration, electrolyte imbalance, cardiac and renal complications
- Treated by loperamide
- Advice
  - Fluids: 8 to 10 glasses a day
  - Diet: (BRAT)
    - BRAT: banana, rice, applesauce and toast (white)
    - noodles, chicken, fish, mashed potato
  - Early reporting of signs of dehydration
- Dose interruptions or reductions in grade 2 or more diarrhoea
Nausea, vomiting, anorexia

• Anti-emetics for treatment
  – Not usually prophylaxis
• Incidence and characteristics
• Dietary advice: eating while on chemo leaflet
  – Little and often
• Dysgeusia (taste alterations)
Gastro-intestinal

• Rare but do occur and must be considered in patients with any presenting symptoms
  – Abdominal Perforation
  – Fistula

• Discontinue drug prior to elective surgery
Blood related

• Myelosuppression
  – Leucopenia, neutropenia
  – Thrombocytopenia

• Thrombo-embolic events
  – Particularly with VEGF pathway drugs

• Haemorrhage
Wound healing

• Impaired wound healing and tissue repair
• Potential increase of post-operative complications
  – Adhesion, perforation and fistula formation,
  – Haemorrhagic and thromboembolic events

• Discontinue prior to elective surgery and dental procedures
Cardiac toxicity

- Cardiac ischaemia, myocardial infarction
- Congestive cardiac failure
- Bradycardia, arrhythmia, Prolonged QT intervals
- Hypertension
  - Baseline assessment and on-going blood pressure monitoring
    - Involve GP
  - Anti-hypertensive medication (aim: less than 140/90 mmHg)
- Some drugs require regular ECG monitoring
- Pay attention to symptoms e.g. reduced exercise, tachycardia at rest
Renal toxicity

• Multiple possible causes
  – Acute injury to renal tubules, damage to renal blood supply, proteinuria

• Proteinuria
  – Harmful impact on renal function
  – Regular urinalysis for early detection

• Electrolyte imbalance
  – Phosphate, magnesium, sodium
  – Monitor and correct
    • Particularly with targeted therapy associated with cardiac effects
Hepatotoxicity

- Increase in ALT and AST
- Increase in bilirubin
- Fatal hepatotoxic events have been reported
- Monitoring: baseline and every 4 weeks
  - Dose modification protocols
    - dose reductions or discontinuation dependent on abnormality
    - increased frequency of monitoring indicated where abnormalities occur
Other effects

• Neurological
  – PRES – encephalopathy syndrome
    • Elevated BP, headaches, altered consciousness, blurred vision, seizures
  – Cerebrovascular events e.g. strokes, intracranial haemorrhage,
    • Monitor, report and act on neurological changes

• Endocrine
  – Hypothyroidism (sunitinib)
  – Hyper and hypothyroidism (others including sunitinib, sorefanib, imatinib and vandetanib)
Other effects

• Fatigue
• Induce and increase depression
• Teratogenic - avoid pregnancy, stop breast feeding
• Pulmonary toxicity
  – Interstitial lung disease, rare but potentially fatal
    • Symptoms – cough and breathlessness
      – With all lung toxicity early identification, treatment cessation and aggressive treatment is vital
• Ocular toxicity - mild to severe
• Buccodental – pain, bleeding, teeth instability
Cautions

• Drug interactions (lots)
  – Pharmacy drug history assessment is really important

• Avoiding grapefruit
  – Increases risk of side effects for some drugs
Priorities of care

• Proactive patient education
• Oral treatment
  – Patient education: Correct administration – time, dose, schedule
  – Instructions (e.g. in relation to food)
    • Often without food to ensure consistent dose due to effect on food of bioavailability
  – Crushing to be avoided (ask pharmacy)
    • Exposure
    • May speed absorption and increase toxicity -
• Early recognition of side effects
• Monitoring at routine visits
Priorities of care

• Inadequate management of side effects
  – Diminish quality of life
  – Decrease adherence to treatment
  – Cessation of treatment that could improve outcomes

• Early intervention and dose reductions can lead to subsequent increase in dose once side effects are controlled
  – Don’t be afraid to report!
  – Advise patients this could help them sustain long-term treatment
New challenges for care

- Decision making around treatment
- Oral treatment, less symptom burden compared with conventional chemotherapy
  - But still with effects that have a significant impact on QOL
  - Getting the balance right
- Significant range of side effects
  - Long term impact emerging and not fully known
    - Some may be reversible, not known about others (e.g. cardiac)
  - Increased survival and people living longer on or following treatment with new therapies
    - Long term monitoring may be needed
Questions?

"Listen, when the side effects of this medication kick in, you'll forget what was wrong in the first place!"