Principles of Cancer Therapy

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Cancer in New Zealand

• Cancer is a common clinical problem in NZ
  – 21,050 new cancer registrations and 8,891 cancer deaths in 2011*

• Learn about the most common types of cancer
  – Top 5 Cancers in NZ*
    1. prostate
    2. colon, rectum and anus
    3. breast
    4. melanoma of the skin
    5. trachea, bronchus and lung
  – The principles of managing common cancers are also relevant to management of less common types of cancer


Clinical presentation of cancer

• Primary tumour
  – Local effects due to expansion (mass), breach of epithelial surfaces (bleeding), narrowing of body tubes (bowel obstruction) or invasion of local structures (hoarseness).

• Metastasis
  – Distant effects of metastatic disease involving lymph nodes (mass), lungs (breathlessness), brain (headache), liver or bone (localised pain).

• Paraneoplastic syndromes
  – Generalised effects due to hormonal (hypercalcaemia), autoimmune (myasthenia gravis) or undefined mechanisms (finger clubbing)
Principles of Cancer Diagnosis and Investigation

• **Diagnosis**
  – Cancer is a pathological diagnosis, requiring tumour biopsy and histopathology to exclude benign pathology, identify tissue of origin, tumour grade and prognostic markers

• **Staging**
  – Determination of extent of involvement according to staging systems, eg. TNM system

• **Functional assessment**
  – Assessment of how patient is likely to cope with the disease and treatment

Principles of Cancer Treatment

• **Key Questions:**
  – Is surgical resection or curative treatment possible? (or will the benefits of therapy be limited to palliation)
  – What treatment modalities are required for the best outcome? (surgery, radiotherapy and chemotherapy)
  – Are different treatment options available? (eg, mastectomy versus lumpectomy plus radiotherapy).

• Multidisciplinary approaches usually required

Principles of Cancer Surgery

• **For Cure**
  – Surgery most effective cancer treatment
    • >40% of cancer is cured by surgery
  – Complete excision with margin of normal tissue

• **Other Indications**
  – Diagnosis (excision biopsy)
  – Staging (assess lymph node spread)
  – Local control
  – Palliation (bypass obstruction)
Principles of Radiation Therapy

- Ionising Radiation Mode of Cell Death
  - Energy from radiation damages DNA (double-strand breaks) and generates free radicals from water that damage membranes, proteins and organelles

- Therapeutic Radiotherapy
  - External beam radiotherapy
  - Planned according to treatment fields, dose to tumour and normal tissue, and number of treatment fractions
  - Component of curative treatment
    - Head and Neck Ca

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Principles of Cancer Chemotherapy

Definition of Chemotherapy:
- using chemicals to kill disease causing cells in the body
- eg. bacteria, fungi, viruses, cancer

In contrast, Drug Therapy:
- using chemicals to modulate body processes
- eg. arterial blood pressure, mood

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Selective Toxicity

- Selective toxicity is the goal of cancer chemotherapy
- Occurs when toxicity is produced in the cancer cell without (or with less) effects in the host cells (cf drug therapy)
- Selective toxicity is achieved by exploiting differences between normal host cells and the disease-producing cells, when:
  - there is an unique target in the pathogen
  - the target is structurally different in the pathogen
  - the target is functionally different in the host
Therapeutic Index (TI)

- important indicator of selective toxicity
- ratio of dose required to produce toxic effect divided by dose required to produce desired effect
- \[ \text{TI} = \frac{\text{ED}_{50} \text{ for unwanted toxicity}}{\text{ED}_{50} \text{ for therapeutic activity}} \]
First Order Kinetics of Tumour Cell Growth and Chemotherapy Killing

- Tumour Growth
  - starts as one malignant cell
  - divides with constant doubling time
  - clinical evident at $10^8$ cells;
  - lethal at $10^{12}$ cells
- Chemotherapy killing
  - Each dose kills a constant proportion of tumour cells
  - repeated doses required
  - Continued after clinical disappearance of disease

Model of tumour growth and response to treatment

Combination Chemotherapy

- more effective than use of single agents
- criteria for combination therapy
  - some activity as a single agent
  - differing mechanisms of action
  - different side-effect profiles
BEP combination chemotherapy for testicular cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>induces DNA breaks</td>
<td>lung</td>
</tr>
<tr>
<td>Etoposide</td>
<td>topoisomerase II poison</td>
<td>bone marrow</td>
</tr>
<tr>
<td>CisPlatin</td>
<td>induces DNA crosslinks</td>
<td>peripheral nerves</td>
</tr>
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Adverse effects of cancer chemotherapy

- Common
- Most related to the main pharmacological action
- Determine the dose and dosing interval of chemotherapy
- May be annoying, dangerous, and limit compliance of patients with therapy
- Most are reversible or clinically manageable, eg. chemotherapy induced nausea and vomiting

Adverse effects of cancer chemotherapy related to pharmacological mechanism

- Antiproliferative
  - myelosuppression, mucositis, alopecia, sterility
- Mutagenesis
  - second cancers, teratogenicity
- Microtubule disturbance
  - peripheral neurotoxicity
- Sex steroid deficiency
  - decreased libido, impotence, flushing
Indications for cancer chemotherapy

- **Cure**
  - High cure rates achieved in acute lymphoblastic leukaemia, testicular cancer, Hodgkin's disease.
- **With surgery**
  - Adjuvant chemotherapy for node-positive breast and colorectal cancers.
- **With radiotherapy**
  - Combined modality therapy for head and neck, cervical cancer etc.
- **Palliation**
  - Improve symptoms and survival time, eg. Lung cancer.

Oncology Clinical Case: Presentation

- Adult ex-smoker
- Cough + haemoptysis for 5 weeks
- Left lung mass on chest x-ray
- Suspected primary lung cancer
- Also, back pain and finger clubbing

CT-guided needle biopsy and pathological diagnosis of non-small cell lung cancer
Staging CT Scans

Mediastinal lymphadenopathy

Investigations and treatment plan

- Assessment Summary
  - Primary non-small cell cancer of left lung with mediastinal lymph node and bone metastases
- Treatment plan
  - Palliation (rather than cure)
  - Radiotherapy to symptomatic bone lesions
  - Palliative chemotherapy with carboplatin and paclitaxel

Chest X-ray showing response to chemotherapy

Before Chemotherapy

After Chemotherapy x3