Principles of Cancer Therapy

Professor Mark McKeage
Dept of Pharmacology & Clinical Pharmacology
The University of Auckland

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, e.g. 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? (e.g., 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

### 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

### 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
- ED$_{50}$ for unwanted toxicity
- TI = \[ \frac{ED_{50} \text{ for therapeutic activity}}{ED_{50} \text{ for unwanted toxicity}} \]

**Pharmacodynamics of cancer chemotherapy**

![Graph showing the relationship between drug concentration and cell killing.]

**Classification of cancer chemotherapy drugs: according to mode of action**

1. Alkylating agents
   - Binds DNA
   - eg. cyclophosphamide
2. Platinum-based drugs
   - Binds DNA
   - eg. cisplatin
3. Antimetabolites
   - Inhibit DNA synthesis
   - eg. methotrexate
4. Topoisomerase-interactive drugs
   - Inhibit topoisomerases
   - eg. doxorubicin
5. Antimicrotubule drugs
   - Bind microtubules
   - eg. paclitaxel
6. Hormonal agents
   - Block production or action of sex steroids
   - eg. tamoxifen
7. Targeted therapies
   - Block oncogenic proteins
   - eg. imatinib
8. Vascular targeting therapies
   - Inhibit angiogenesis
   - eg. bevacizumab
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

- 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>
</tbody>
</table>

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